Osteoporosis in the elderly, pharmacological and non pharmacological prevention and treatment

Esther Kamau

Degree Thesis

Human Ageing and Elderly Services

2011

Förnamn Efternamn

DEGREE THESIS	
Arcada	
Degree Programme:	Human Ageing and Elderly Services
Identification number:	8274
Author:	Kamau Esther Wambui
Title:	Osteoporosis in Postmenopausal elderly women and elderly men (65+), pharmacological prevention and treatment of associated fractures.
Supervisor (Arcada):	Solveig Sundell
Commissioned by:	Osteoporosis Prevention and Age Concern (Kenya)

Abstract:
The aim of this study is to highlight and identify osteoporosis in the elderly as well as to analyze on the current risk factors causing osteoporosis and pharmacological prevention and treatment. This study has three research questions, question one is: What are the current risk factors that cause osteoporosis in the elderly and can they be changed? Question two: What are the classifications of osteoporosis medications and their effects on the disease? And question three is: What are the current approved medications for osteoporosis and their methods of administration? Studies used in the literature review of this thesis included elderly people from all races.The method chosen was literature review. Previous researched articles of relevance to effectiveness, acceptability and ethical issues were sought. It can be concluded that osteoporosis prevention requires adequate calcium and vitamin D intake, regular physical activity, and avoiding smoking and excessive alcohol ingestion, intake of proper nutrition and living a healthy life style. Risk of fracture determines whether medication is also warranted. A previous vertebral or hip fracture is the most important predictor of fracture risk. Bone density is the best predictor of fracture risk. Age, weight, certain medications, and family history also help establish a person's risk for osteoporotic fractures. All women should have a bone density test by the age of 65 or younger (at the time of menopause) if risk factors are present. Guidelines for men are currently in development. Medications include both antiresorptive and anabolic types. Antiresorptive medications estrogens, selective estrogen receptor modulators (raloxifene), bisphosphonates (alendronate, risedronate, and ibandronate) and calcitonins work by reducing rates of bone remodeling. Teriparatide (parathyroid hormone) is the only anabolic agent currently approved for osteoporosis in the United States. It stimulates new bone formation, repairing architectural defects and improving bone density. All persons who have had osteoporotic vertebral or hip fractures and those with a bone mineral density diagnostic of osteoporosis should receive treatment. In those with a bone mineral density above the osteoporosis range, treatment may be indicated depending on the number and severity of other risk factors.

Keywords:	Osteoporosis,prevention,treatment,medication,drugs,therap-eutics,ageing
Number of pages:	88
Language:	English

Date of acceptance:	

OPINNÄYTE	
Arcada	
Koulutusohjelma:	
Tunnistenumero:	
Tekijä:	
Työn nimi:	
Työn ohjaaja (Arcada):	
Toimeksiantaja:	

Tiivistelmä:

Kirjoita koko opinnäytteesi tiivistelmä tähän. Tekstin tulee olla sellaisenaan ymmärrettävä kuvaus tehdystä tutkimuksesta, ja siksi sen täytyy olla huolellisesti harkittu ja viimeistelty. Asiaa tuntemattomankin lukijan on saatava selkeät ja asialliset tiedot siitä, mitä opinnäyte käsittelee, mitä menetelmiä on käytetty ja minkälaisia tuloksia on saatu. Tiivistelmässä ei saa olla mitään sellaisia asioita, jotka eivät käy ilmi myös opinnäytteestä. Siinä ei myöskään tule olla mitään tarpeettomia selityksiä tai täytevirkkeitä.

Tiivistelmän tulee esitellä tutkimuksen tarkoitus, tutkimusongelma, tehtävärajaus, aineisto, käytetyt menetelmät, tärkeimmät viitteet sekä tulokset ja niiden pohjalta tehdyt päätelmät ja toimenpidesuositukset. Aluksi kuvataan lyhyesti aikaisempia tutkimuksia, teorioita tai käytännön tarpeita, joiden perusteella opinnäytteen kysymyksenasettelu on syntynyt.

Tekstin pituus on 200−300 sanaa, ja se voidaan usein asetella yhdeksi kappaleeksi. Aikamuotona käytetään preesensiä tai imperfektiä.

Loppuun kirjoitetaan 4−8 avainsanaa, jotka antavat tiivistelmää silmäilevälle vihjeen opinnäytteen sisällöstä. Jos opinnäyte on yritykselle tehty tilaustyö, on yrityksen nimi yksi avainsanoista.

Avainsanat:	
Sivumäärä:	
Kieli:	
Hyväksymispäivämäärä:	

Table of Contents

Figurer / Figures

Tables

1. INTRODUCTION

Osteoporosis is a disease characterized by low bone mineral density and structural deterioration of bone tissue leading to bone fragility and increased cases of fractures particularly of the hip, spine and wrist.

Osteoporosis results from reduced bone mineral density. It has enormous impact on public health and on the quality of life of the elderly (Goltzman David 2008). Osteoporosis is one of the major cases of disability, morbidity and mortality in older people. It is a current world wide socioeconomic problem with an increasing severity and frequency due to the progressive aging of the world's population. The health of the bones depends on the genes, the level and hormones in the body, how physically active the body is and what an individual eat. There are also other factors that cause the decrease of bone density causing osteoporosis. Some of the causes can be controlled while others cannot be controlled

Osteoporosis is a disease in which the bones become weak and more likely to break. People with osteoporosis most often break bones in the hip, spine and wrist. This condition can cause pain, difficulty in breathing, a loss of independence and even death when complications occur from some fractures. Breaking of bones can be caused from minor falls or in serious cases from simple action such as sneeze or bumping into furniture (National Osteoporosis Foundation)

Osteoporosis is a chronic progressive disease of multi factorial. It is the most common metabolic bone disease in the United States. It has been most frequently recognized in elderly white women, although it does occur in men and women, all races, and all age groups. This disease is considered a "silent thief" that generally does not become clinically apparent until a fracture occurs. Screening at-risk populations is therefore essential (Kosmin, 2011)

As one age, bone mass tend to decline due to a variety of factors. Osteoporosis or osteopenia which is an early warning sign, signals an imbalance in the remodelling signal. Too much bone is broken down and too little new bone is built back this result to brittle bones which are prone to fracture. A combination of causes is often to blame for bone loss (Buffum, 2011)

The body is constantly at work breaking down and rebuilding the bones. Specialized bones called osteoblast pull calcium, magnesium and phosphorous from the blood to build bone mass. Usually the body does not show any symptoms of osteoporosis until a fracture occurs or a vertebra collapses causing a loss of height and a hump in the back.

.

1.1 Statistics

Osteoporosis is a recognized major public health problem in both developed and developing countries. As the age span has increased, osteoporosis has become the fourth most common disease in aged adults. Due to the high degree of morbidity and mortality associated with fracture, prevention of such events is imperative because the number of women at risk for osteoporosis is expected to rise dramatically with the aging world population. It has been estimated that the total medical care costs for osteoporosis in Europe including hospitalization and rehabilitation were 36.3 billion Euros in 2000 and the corresponding projected costs in 2050 will be 76.8 billion Euros, this is more than double. Worldwide projections estimate the number of hip fractures by 2050 could range between 7.3 and 21.3 million with a corresponding cost of 100 billion Euros. (Dontas, 2007)

From many studies, it is clear that there are several risk factors that cause osteoporosis. Statistics shows that there are 75 million people in Europe, USA, and Japan that are affected by osteoporosis. For the year 2002, there were estimated 9 million new osteoporotic fractures of which 1.6 million were at the hip, 1.7 million were at the fore arm and 1.4 million were clinical vertebral fractures. Europe and America accounted for 5.1 per-

cent of all these fractures (International Osteoporosis Foundation). In the year 2002, there were estimated almost 44 million women and men in the states with either osteoporosis or low bone mass which is a condition of thinning bones that increases an individual risk for developing osteoporosis. In New York State alone, 3 million men and women have osteoporosis or low bone mass. In the United States nearly one of every two Caucasian or Asian women over fifty will experience a fracture as a consequence of osteoporosis. Men and women of other ethnic groups have a slightly lower but still substantial risk for fracture. While it is typical to lose some bone mass as one age, it is not a normal thing to develop osteoporosis, to experience painful fractures or to lose more than one to a half inches of height. (Hayes, 2003)

As the global population ages, the prevalence of age related osteoporosis this is postmenopausal osteoporosis, male osteoporosis and related fractures is likely to increase considerably. In the US, the prevalence of osteoporosis is expected to grow from an estimated 10 million in 2002 to 14 million by 2020. In the EU, the total number of hip fractures is estimated to increase from 414 000 to 972 000 from year 2000 to 2050 ((National Osteoporosis Foundation 2005)

Vertebral fractures are estimated to increase during this time from 23.7 million to 37.3 million. The economic consequences of osteoporosis with its associated morbidity and mortality due to fractures are staggering. While total world-wide estimates are not readily available, there are data that describe the costs in various countries. In Belgium (population ~10 million), the total cost of hip fractures in 1996 was almost 126.2 million U.S dollars per year (Reginster et al 1999). The estimated cost of osteoporotic fractures in females greater than 50 years of age using 1997 figures cost the UK 727 million pounds and 1.23 billion U S dollars or an estimated 942 million 1.6 billion U S dollars including men, assuming the cost of treatment was the same as females. The annual cost of osteoporotic fractures to the US healthcare system in 2001 was approximately17 billion U.S dollars, with a single hip fracture costing approximately 40 000 U.S dollars (National Osteoporosis Foundation 2004).

In Kenya prevalence of osteoporosis in post-menopausal women is about 24.3 per cent as compared to 0.9 per cent in pre-menopausal women. Prevalence of osteopenia is reported to be 32 per cent and 20.5 per cent in post and pre-menopausal women respectively. (Odawa , Ojwang , Muia , *et al,* 2004)

More women die from osteoporosis related fractures than from breast cancer, cervix and uterus cancer combined. Osteoporotic fractures are the cause of 200,000 deaths annually in the U.S which is about one tenth of all deaths. Health cost in 2002 for osteoporotic fractures alone was 18 billion dollars (Karmen, 2011)

Since this is an alarming issue in the society today. The most logical thing the world should do is trying and prevents the bone from losing its density. In order to know how to do that, one must be able to identify or detect the risk factors that cause osteoporosis

Osteoporosis has been shown in the studies to have large genetic components. A parental history of fracture confers an increased risk of fracture that is independent of bone mass density (International Osteoporosis Foundation). Major factors include low body mass index, female sex, older age, family history of hip fracture, patient history of fragility fracture, use of steroids, auto immune disease, secondary causes of osteoporosis, smoking, more than three alcoholic drinks a day and low bone mass in the hip region (Karis 2005). Many people with osteoporosis have several risk factors but others who develop have no known risk factors. There are some risk factors which can be changed while others cannot be changed (e med TV 2006)

Calcium is essential for maintaining the health of the bones but cannot guarantee the health of the bones completely. Many studies show that certain foods are more effective than the pill supplements to maintain bone density.

Eating a well balanced diet rich in calcium and getting adequate vitamin D, engaging in regular exercise and making healthy lifestyles choices will promote healthy bones (Hayes 2003). Individuals that exercise regularly, expose themselves to healthy amount of sunshine and eat a whole foods diet based around dark green leafy vegetables, fruits, beans, nuts, seeds and lean sources of proteins are taking the right steps towards osteoporosis prevention (Hottinger Greg). The role ethnicity plays in the incidence and prevalence of osteoporosis is connected to genetics and is also integral to other risk factors, such as nutrition and physical activity.

2. AIMS AND RESEARCH QUESTIONS

The significance of this study is to discuss osteoporosis disease in the elderly (65+), and to identify and review pharmacological and non pharmacological prevention and treatments. This paper also provides important information about the adverse effect of several factors on the bone health and which factors can be changed and which cannot be changed. This paper also attempt to explain how osteoporosis medications that are approved by the Food and Drug Administration (FDA) are classified in categories according to their different purposes on the disease and also oh how they should be administered to patients.

2.1 Research questions

1. What are the current risk factors that cause osteoporosis in the elderly and can they be changed?

2. What are the current approved osteoporosis medications and how they have been classified according to their purpose?

3. What are the methods of administration for these medications?

3. THEORETICAL BACKGROUND

This Chapter explores the various medical contents of previous researches on the independent variables present in this study. From this chapter, we get a clear understanding of bone cells, bone remodeling processes and how deterioration of bone mineral density leads to osteoporosis from a medical perspective. This chapter also explains the different levels of osteoporosis and some of the theories about osteoporosis

In the 1930s, osteoporosis became an object of clinical engagement to the American physician Fuller Albright during his study in Germany. In the 1940s, Albright imported his interest in osteoporosis from Germany to United States (Nordin Christopher 2004)

In the medical literature, osteoporosis is currently presented as a major global public health problem, one that has already been proposed as the disease of the twenty-first century (Clark 2002). As a consequence of its current medical definition, approximately 200 million women worldwide are described as having osteoporosis In modern medicine, osteoporosis is understood as a skeletal disorder characterized by decreased bone mass, leading to an increased risk for fracture of the hip, spine, wrist, and other skeletal sites (Lane 2006).

Not only has osteoporosis been attributed an important role in the causation of fractures but it is also seen as a major killer. This is because hip fractures are perceived as causing what in medical terms is described as an excess mortality among the aged. With an increasing longevity in the world population (Cummings and Melton 2002), Proper understanding of the morphological degeneration in osteoporosis requires knowledge of the remodeling processes. These processes are conducted by specialized bone-resorbing cells (osteoclasts) and bone-forming cells (osteoblast). (Ruimerman Ronald 2005)

The modeling and remodeling processes are not very different at the cellular level. They are based on the separate actions of bone resorbing cells called osteoclasts and bone forming cells called osteoblasts. The remodeling process begins at a quiescent bone surface with the appearance of osteoclasts. These are large multinucleated cells that form by fusion of mononuclear precursors of haemotopoetic origin (Ruimerman Ronald 2005)

Osteoclasts are large multinucleate cells this are cells with more than one nucleus that differentiate from another type of cell called a macrophage. In normal bone, bone formation and bone resorption are closely coupled processes involved in the normal remodeling of bone. In osteoporosis, the net rate of bone resorption exceeds the rate of bone formation, resulting in a decrease in bone mass without a defect in bone mineralization.

In women, osteoclast activity is increased because of decreased estrogen after the menopause. Men with prematurely decreased testosterone may also have increased osteoclast activity. These changes result in further net loss of bone. The amount of bone available for mechanical support of the skeleton eventually falls below the fracture threshold and one may suffer a fracture with little or no trauma. (http://www.medterms.com/script/main/art.asp?articlekey=11794)

Osteoclasts are a type of bone cell that removes bone tissue by removing its mineralized matrix and breaking up the organic bone (organic dry weight is 90% collagen). This process is known as bone resorption. Osteoclasts were discovered by Kolliker in 1873. They are active mostly on the surface of cancellous bone or the spongy tissue and in cortical bone. Osteoblasts are the cells that create the bone tissue that lay down the minerals. The resorption/removal process is faster than the laying down of new bone by osteoblasts, so an increase in bone formation and remodeling overall results in a loss of bone mass, when it occurs in adults. Glucocorticoid drug use and other physiological conditions such as chronic inflammatory disorders and thyroid hormone problems can contribute to the risk of bone fracture. (Latina Health Projec 2009-2011)

Osteoblasts are bone cells that make bone. It does so by producing a matrix that then becomes mineralized. Bone mass is maintained by a balance between the activity of os-

teoblasts that form bone and other cells called osteoclasts that break it down (Medicine Net.com).

Osteoporosis can affect almost the entire skeleton. It is a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility. The disease often does not become clinically apparent until a fracture occurs. Osteoporosis represents an increasingly serious problem in the United States and around the world. Many individuals, male and female, experience pain, disability, and diminished quality of life as a result of having this condition. The economic burden the disease imposes is already considerable and will only grow as the population ages **(**Kosmin Dana Jacobs 2011)

Despite the adverse effects of osteoporosis, it is a condition that is often overlooked and under treated in large part because it is so often clinically silent before manifesting in the form of fracture.

A Gallup survey performed by the National Osteoporosis Foundation revealed that 75 per cent of all women aged 45-75 years have never discussed osteoporosis with their physicians. Failure to identify at-risk patients, to educate them, and to implement preventive measures may lead to tragic consequences. It is a preventable disease that can result in devastating physical, psychosocial, and economic consequences. Prevention and recognition of the secondary causes of osteoporosis are first-line measures to lessen the impact of the disease. (Kosmin Dana Jacobs 2011)

3.1 Types of osteoporosis

3.1.1 Postmenopausal osteoporosis

The process of bone loss proceeds much more rapidly after menopause. Postmenopausal bone loss is the results of increased bone desorption or in other term high turnover related to the reduction of estrogens production. Approximately 10 - 15 years after menopause the initially accelerated bone metabolism normalizes and mainly age-associated

processes affect bone mass evolution. Postmenopausal osteoporosis and age-associated osteoporosis are referred to as primary osteoporosis type I and type II, respectively (Kosmin Dana Jacobs 2011)

Table 1.Diagnostic categories for osteoporosis in postmenopausal women based on World Health Organization criteria

Category	Definition by bone density
Normal . Osteopenia	A value for BMD that is not more than 1 SD below the young adult mean value A value for BMD that lies between 1 and 2.5 SD below the young adult mean value.
Osteoporosis .	A value for BMD that is more than 2.5 SD below the young adult mean value
Severe osteoporosis	A value for BMD more than 2.5 SD or below the young adult mean in the presence of one or more fragility fractures

.
Abbreviations: BMD, bone mineral density; SD, standard deviation. (Srivastva.Manish MD, Chad Deal. MD Osteoporosis in elderly: prevention and treatment, Clin Geriatric Med 18 (2002) 529– 555)

3.1.2 Primary osteoporosis

Primary osteoporosis occurs in patients, in whom a secondary cause of osteoporosis cannot be identified, including juvenile and idiopathic osteoporosis. Idiopathic osteopo-

rosis can be further subdivided into postmenopausal (type I) and age-associated or senile (type II) osteoporosis. Juvenile osteoporosis usually occurs in children or young adults of both sexes. Type I osteoporosis (postmenopausal osteoporosis) occurs in women aged 50-65 years. This type of osteoporosis is characterized by a phase of accelerated bone loss. This bone loss occurs primarily from trabecular bone. In this phase, fractures of the distal forearm and vertebral bodies are common. Type II osteoporosis (age-associated or senile) occurs in women and men older than 70 years. This form of osteoporosis represents bone loss associated with aging. Fractures occur in cortical and trabecular bone. In addition to wrist and vertebral fractures, hip fractures are often seen in patients with type II osteoporosis (Kosmin Dana Jacobs 2011)

3.1.3 Secondary osteoporosis

When osteoporosis occurs as a consequence of specific other diseases such as adrenal insufficiency, hyperthyroidism, hypogonadism, liver diseases or immobility, or if it results from corticosteroid treatment, it is also termed as secondary osteoporosis. (Roche Diagnostics 2009)

As bones become more brittle with age due to bone mass loss, there is a greater risk of incurring a fracture. In the course of their lives, approximately 40 percent of women and about 10 - 15 percent of men suffer a fracture, especially of vertebral bodies, the femur and the forearm. The estimated incidence of femoral neck fractures is about 1.66 million per year worldwide. As life expectancy increases, the incidence of osteoporosis will increase four fold. (Roche Diagnostics 2009)

3.2 Bone pathophysiology

Osseous tissue, or bone tissue, is the major structural and supportive connective tissue of the body. Osseous tissue forms the rigid part of the bone organs that make up the skeletal system. (Wikipedia) The bone tissue is composed of inorganic 70 percent, organic 22 percent and water 5 to 8 percent. Inorganic matter includes calcium hydroxyapatite 95 percent and impurities 5 percent. Organic matter is composed of type 1 collagen 85 percent, other collagen and non colagenous proteins, which are(osteopontin, fibronectin, peptide growth factors and osteocalcin) and cells which are (osteoblasts, osteoclasts and osteocytes) (Rizzoli R 2005)

Cortical bone accounts for 80 percent of bone skeleton and 20 percent of bone surface. It is found in shafts of long bones and outer surfaces of flat bones. Trabecular (spongy and cancellous) bone accounts for 20 percent of adult skeleton and 85 percent of bone surface. It is found at the end of long bones and inner parts of flat bones (Rizzoli R. second edition 2005; 1-4)

Bone microstructure refers to trabecular thickness, spacing, connectivity and structural index. Early alteration in the micro architecture includes perforation and disappearance of trabeculae without major affects of body mass density. (Amman P. and Rizzoli R 2003; 14 (suppl 3):513-518)

Determination of bone strength includes bone geometry, cortical thickness, porosity, and trabecular bone morphology, intrinsic properties of bone tissue and rate of bone remodeling. Body mass density which refers to density (mass per area rather than per volume), corresponds to the ratio between bone mineral content and bone scanned area. It is the major determinant of bone strength. Degree of mineralization also determines strength (Rizzoli R. 2005)

Bone remodeling process is a surface based phenomenon that involves the removal of a quantum of bone by osteoclasts followed by the deposition of new bone by osteoblasts within the cavity formed. Knowledge of remodeling is essential to understand pathophysiology of osteoporosis. The primary function of bone remodeling is repair of micro damage and supply of calcium to maintain serum calcium levels. (Kasper D.L, Fauci A. S, Congo D. L, et al)

The remodeling cycle has four phases namely; resorption, reversal, formation and quiescence. Resorption phase takes 10 to 14 days while formation phase takes 150 days. During resorption phase 1 modeling, osteoclast recruitment, differentiation, activation and attraction to site of resorption occurs. During bone formation (phase 3 remodeling), osteoblasts undergo recruitment, differentiation and activation. They produce osteoid which later becomes calcified to mature bone. Some osteoblasts become trapped within the matrix and differentiate into osteocytes. Other differentiate into flattened lining cells that cover the bone surface while the rest undergo apoptosis (Kasper D.L, Fauci A. S, Congo D. L, et al) and (Ralston S.H 2001)

Estrogen inhibits osteoclasts and stimulates osteoblasts. Osteblasts produce many growth factors and cytokines that mediate estrogen action. The result of estrogen deficiency is increased osteoblast recruitment and perhaps activities (Compston J. E 2001; 81:419-447)

A fracture is considered to be osteoporotic (fragility fracture) if it is caused by relatively low trauma, such as a fall from standing height or less; a force which in a young healthy adult would not be expected to cause a fracture.

Overwhelming evidence has shown that the incidence of fracture in specific settings is closely linked to the prevalence of osteoporosis or low bone mass. In a prospective study of 8134 women older than 65 years in age, the study showed that the women with BMD of the femoral neck in the lowest quartile have 8.5-fold greater risk of sustaining a hip fracture than those in the highest quartile (Deplasl A et al 2004)

A fragility fracture (FF) is the clinically apparent and relevant (adverse) outcome in osteoporosis. Fragility fractures are fractures that result from low-level trauma, which means mechanical forces that would not ordinarily cause fracture. (Chrisopoulos Sadhana Bose Sergio 2010)

Hip fractures are already a major public health problem and this situation is expected to worsen in the future. They give rise both to suffering among patients and to a major economic burden on society in terms of cost of care. Hip fractures among the elderly are almost always caused by falling. As in other age groups, the reasons for falls among the elderly are multifactorial and relevant factors may depend on the individual, his or her environment, or his or her social circumstances. In contrast to other age groups, hip fractures are more common among elderly women than men, with women accounting for 75% of cases. (Furugren Lena and Laflamme Lucie 2007)

A vertebral compression fracture occurs when the bones of the spine become broken due to trauma. Usually the trauma necessary to break the bones of the spine is quite large. The vertebrae most commonly broken are those in the lower back (emedicine-health 2011). Most studies have shown that there is an exponential rise in the number of fractures with aging. In the European Vertebral Osteoporosis Study, the prevalence of vertebral deformity was 10 per cent in men age 50 to 54 years, rising to 18 per cent at age 75 to 79 years. In women age 50 to 54 years, the prevalence was only 5per cent; however, this rose to 24 per cent at age 74 to 79 years. Similar results were reported from other studies (Srivastava & Deal 2002)

3.3 Theories about Osteoporosis

In the past, people thought a shortage of estrogen caused osteoporosis. People thought this because most patients were women who came down with osteoporosis after menopause, and because estrogen does influence the bone-forming activity of osteoblasts. However, close research has found that decline in estrogen levels is not a major cause of osteoporosis. Estrogen acts through two receptors called ERa and ERb. Osteoblasts express ERb, but it isn't clear that ERb agonists promote bone density. Estrogen supplements were given to post menopausal women to reduce risk of osteoporosis and for other reasons. This practice is employed much less now because the benefits of estrogen do not seem to outweigh the risks.

There are conflicting theories about the cause of osteoporosis. Many researchers believe that it is brought on by faulty diet and lifestyle habits. Root causes, in addition to smoking, are inactivity, poor diet, hormone deficiencies and imbalances, heredity and others. Uses of certain medications, such as antacids, thyroid, lithium, lasix, and chemotherapy are contributing causes. Certain drugs, such as steroids, like prednisone, may increase the risk of osteoporosis. This includes inhaled steroids for asthma or COPD. (Alice E. Marson2010)

New research reveals why you should not clip your cell phone to your belt or pocket. The research warns that wearing a cell phone on your waist or hip may weaken an area of your pelvis. Researchers found that bone density is lowered on the side where the mobile phone is carried. Bone density can be affected by electromagnetic fields emitted by a cell phone. (Marson Alice E. 2010)

3.4 BMD assessment methods

Osteoporosis is a disease in which screening of asymptomatic individuals may be beneficial because it has a long preclinical course before the onset of fracture and because of the availability of both a reliable test to establish the diagnosis and treatments that have

been shown to reduce the risk of fractures. General consensus exists regarding recommendation that osteoporosis screening with BMD measurements should be individualized, but how this individualized approach to screening should be achieved remains controversial. There are several ways of assessing and screening.

Bone densitometry is a medical term referring to the amount of matter per cubic centimeter of bones. Bone density (or BMD) is used in clinical medicine as an indirect indicator of osteoporosis and fracture risk (Wikipedia). Bone densitometry is an established method for assessing osteoporosis. A variety of different methods have been developed over the past 25 years. The two most commonly used methods are dual energy x-ray absorptiometry (DEXA) and quantitative ultrasound. DEXA is recommended and FDA approved for BMD measurement; it is precise, noninvasive, has low radiation exposure, and takes 10 minutes to administer. Because annual losses of bone mass normally seen with aging range from 1 per cent per year, the precision error of current instruments (approximately 1 per cent to 2 per cent with DEXA) cannot provide reliable information at intervals shorter than 2 years. Therefore, if follow-up studies are desired, a minimum interval of 2 years is recommended. Exceptions to this include high dose steroid therapy that can result in rapid bone loss in a shorter interval (6 to 12 months) The National Osteoporosis Foundation has published recommendations for BMD screening using DEXA (Srivastava, Deal 2002)

A bone densitometry scan is a special type of X-ray test used to measure the calcium content of the bone, usually in the lumbar region (the lower back) and the hips. The examination is also called a DEXA-scan, QDR-scan or BMD (bone mineral density) measurement. (Burnett & Pillinger 2005)

Body Mass Density is one of the most important risk factor for fracture of substantial importance (Kanis J. A. & Gluer C.C 2001).

Central hip and spine measurement by DEXA should be used for both risk assessment and follow up as they provide the most accurate and precise measurement of BMD. Hip is the preferred site in most individuals. Spine BMD may be the most sensitive indicator of bone loss in young individuals. The second way of measuring bone density is by quantitative computed tomography which is primarily used to the spine. Unlike DEXA, it can provide a true density (mass of bone per unit volume) since it is three dimensional

and it specifically analyses trabecular bone in vertebrae, eliminating posterior cortial elements of the spine. (Johnnell & Brit. 1996)

The use of biochemical bone turnover markers (BTMs) in clinical trials has been helpful in understanding the mechanism of action of therapeutic agents. However, their role in the care of individual patients is not well established. Biologic and laboratory variability in BTM values have confounded their widespread use in clinical practice. BTMs have little value for the diagnosis of osteoporosis, because dual-energy x-ray absorptiometry (DXA) is far superior for this purpose. However, markers of bone turnover give some indication about the future risk for bone loss and fractures. More importantly, they are useful in monitoring the efficacy of antiresorptive therapy in patients with osteoporosis. (Rosen, Clifford, Mulder 2011)

Women who have borderline low BMD and elevated markers are at increased risk of losing bone health in the near future and may be candidates for pharmacologic intervention. The resorption markers are also independent risk factors for fracture. (Srivastava, Deal, 2002)

FRAX is a Web-based algorithm designed to calculate the 10-year probability of major osteoporosis-related fracture (clinical vertebral, hip, forearm, or humerus) and hip fractures in men and women based on easily obtained clinical risk factors and bone mineral density (BMD) of the femoral neck. The NOF updated its U.S. guidelines in 2008 to incorporate FRAX and provide recommendations for its use in clinical practice. As recommended by the NOF, FRAX should be used when the decision to begin pharmacological treatment is uncertain. Patients meeting the following criteria are appropriate candidates for using FRAX to assist with a treatment decision: men aged 50 years and more and postmenopausal women, who are not on treatment and who have low bone mass (T-score between - 1.0 and - 2.5), no prior hip or vertebral fracture (clinical or morphometric), and an evaluable hip for dual x-ray absorptiometry (DXA) study. Although BMD is not required for the FRAX algorithm, the NOF recommends using FRAX plus BMD for treatment considerations. If femoral neck BMD is not available, total hip BMD may be substituted, but use of BMD from sites other than the hip is not recommended (Nelson, Watts, 2010)

In the general population, previous fracture is an important risk factor for subsequent fracture. Using clinical and claims data from the USRDS, it has been reported that a history of any fracture resulted in a hazard ratio of 8.33 (5.04–13.74) for hip and 7.32 (3.41– 15.71) for vertebral fracture and symptomatic vertebral fracture was associated with a more than sevenfold increased risk of subsequent fracture. Therefore a lateral X-ray of the spine to evaluate for prevalent fracture may be a useful indicator of future fracture risk in CKD-5D (Toussaint, Elder, Kerr 2010)

Quantitative computed tomography (QCT) has been used to determine BMD in CKD-5D and can be used to distinguish BMD values in both cortical and trabecular bone compartments, while avoiding artifacts of vascular calcification and local degenerative changes that bedevil.
DEXA evaluation sites (radius and tibia) as well as central sites (lumbar spine and proximal femur) (Toussaint, Elder, Kerr, 2010). Although multiple technologies are available for measurement of BMD, central dual-energy x-ray absorptiometry (DXA) of the hip (femoral neck or total hip) is the gold standard for diagnosing osteopenia or osteoporosis (Mauck, Clarke 2006; 81(5):662-672)

4. ELDERLY AND OSTEOPOROSIS RISK FACTORS

Risk factors are characteristics that increase the chances of developing a certain condition or disease. Risk factors for osteoporotic factors include age, gender, race, geographical region, diet, lifestyle, hormonal status, bone density, bone quality, body mass index and medical co morbidities (Table 2).

Table 2. Clinical Risk Factors Included
In the World Health Organization
Fracture Risk Assessment Tool (FRAX)

- Country of residence
- Ethnicity (U.S. models only: Caucasian, black, Hispanic and Asian)
- Age (allows ages between 40 and 90 years)
- Sex

- Weight and height for calculating body mass index
- Prior fragility fracture, including radiographic vertebral fracture
- Family history of osteoporosis (parent with hip fracture)
- Current smoking
- Glucocorticoid use (prednisolone 5mg or more daily for 3 months and more, current or past)
- Rheumatoid arthritis (physician-confirmed diagnosis)
- Alcohol use (3 units daily or more)
- Secondary osteoporosis
- Bone mineral density, model also works without bone mineral density (Nelson, Watts, 2010)

4.1 Age

‘

Fracture risk is much higher in the elderly than in the young. The frequency of hip fractures in particular increases exponentially with age, especially after the age of 70, in both men and women, in most regions of the world. This increase in fracture risk is considered to be due to both the age-related decrease in bone mineral density of the proximal femur and the age-related increase in falls, and is also related to the increased co morbidities of the elderly. (Dontas, Yiannakopoulos, 2007)

BMD decreases and as a consequence the risk of osteoporosis increases with age. A significant increase in prevalence with each decade after age 60 has been demonstrated. The United States National Health and Nutrition Survey (NHANES) III survey of postmenopausal women showed that the prevalence of osteoporosis in non-Hispanic white American women was 27 per cent (50-59 years), 32 per cent(60-69 years) and 41 per cent for those70 years. A Previous estimate based on data from Rochester, Minnesota indicated a lower (though still high) prevalence – 14.8 per cent (age 50-59 years), 21.6 per cent (aged 60-69 years), 38.5per cent (70-79 years) and 70per cent (80 years.)A Yorkshire based study showed a prevalence of 24 per cent in women aged 60-69 years (Scottish Intercollegiate Guidelines Network 2005)

4.2 Hormonal factors – gender differences

Peak bone mass for women is lower than that one of men The increased bone loss in women after menopause and their increased propensity to falls compared to men, eventuates that the incidence of hip fractures in women of any age in the USA and Europe is about twice that of men at any age. In addition, because women live longer than men, more than 75 per cent of all hip Fractures are presented in women. Most researchers report a 2:1 ratio of female: male hip fracture incidence over the age of 65. Other hormonal factors that increase fracture risks are premature menopause, primary or secondary amenorrhea, hyperthyroidism, hyperadrenocorticism and primary and secondary hypogonadism in men (Dontas, Yiannakopoulos, 2007). In females, the timing of the menopause and subsequent oestrogen deficiency can also affect the rate of bone loss. Similarly, men who are hypogonadal may have increased rates of bone loss and higher fracture rates in later life. (Anne Sutcliffe, 2005)

Women are at greater risk of osteoporosis as they have smaller bones and hence lower total bone mass. Additionally, women lose bone more quickly following the menopause, and typically live longer. Osteoporosis is less common in men but is still a significant problem. The rate of bone loss in men is less than that in women. In the Framingham Osteoporosis Study annualized percent bone loss for women was 0.86 per cent to 1.21 per cent at different sites and for men, 0.04 per cent to 0.90 per cent. Secondary causes of osteoporosis are, however, more common in men, affecting approximately 40 per cent of cases. Accepting reproductive factors and taking into account the increased influence of secondary factors in men, the risk factors in women also apply to men (Scottish Intercollegiate Guidelines Network, 2005)

4.3 Demographic factors

Northern countries appear to have an increased incidence compared to southern ones. Fracture incidence has been reported to be higher in white Scandinavian women than in North American women of comparable age. The lifetime risk of any osteoporotic fracture at the age of 50 years has been estimated to be 46 per cent in women and 22 per cent in men in Sweden, with corresponding figures of 40 per cent and 13per cent in the USA. In addition, the lifetime risk and the age-specific risk of a hip fracture among

black men and women is approximately 50 per cent of that among white men and women. In India, osteoporotic fractures have a higher male to female ratio than among Westerners (Dontas, Yiannakopoulos, 2007)
Afro-Caribbean women have a higher BMD than white women at all ages due to a higher peak bone mass and slower rate of loss. White women have a 2.5-fold greater risk of getting osteoporosis (Scottish Intercollegiate Guidelines Network 2005)

4.4. Medical and family history

In families, bone mass is often lower in young women whose mothers have sustained osteoporotic fractures (Anne Sutcliffe, 2005)

Fracture risk factors include a previous fragility fracture, family history of fracture or genetic factors, low bone mineral density, low body mass index, weight loss, resting pulse rate over 80 beats per minute, rheumatoid arthritis, use of corticosteroids, anticonvulsants, loop diuretics, and liability to falls (e.g., due to neuromuscular, cardiovascular and vestibular disorders, poor vision, dementia, use of certain drugs and polypharmacy) (Dontas, Yiannakopoulos, 2007)

Lower BMD is found in women and men with a family history of osteoporosis, a family history being defined as a history of osteoporosis or brittle bones, kyphosis, or low trauma fracture after age 50 years. Individual BMD decreases as the number of family members with osteoporosis increases. Overall family history is a more sensitive predictor of osteoporosis risk than maternal or paternal history alone Prevalence of a positive history in sisters is similar to prevalence reported for mothers. In one epidemiological study the greatest risk of categorical osteopaenia was in patients whose father had a history of osteoporosis (Scottish Intercollegiate Guidelines Network 2005)

4. 5 Lifestyle risk factors

All persons should be accustomed to a healthy balanced diet and a physically active lifestyle beginning from childhood and continuing throughout life, for normal skeletal

growth and aging. Adequate calcium intake has been demonstrated to be significant for increasing and maintaining bone mass. The importance of vitamin D for the intestinal absorption of calcium is also well documented. Hence, inactivity or immobilization, low dietary calcium intake, vitamin D deficiency, as well as cigarette smoking, caffeine intake, excessive alcohol consumption, and liability to falls, consist lifestyle risk factors for osteoporotic fractures (Dontas, Yiannakopoulos, 2007)

4.6 Genetics

Genetic factors account for as much as 80 per cent of the variance in peak hone mass and also influence the rate of bone loss. Studies demonstrate that genetic factors play an important role in regulating bone density, skeletal geometry and bone turnover as well as contributing to the pathogenesis of osteoporotic fracture itself (Anne Sutcliffe, 2005)
The strong association between body mass and peak bone mass may partly result from shared genetic influences. (Chaudhri Tauseef, 2006)
There is a genetic component to osteoporosis and having a parent with the condition or a history of hip fracture puts a person at greater risk of fracture. (Elliott Mary, 20111)

4.7 Nutrition

Like any organ in the body, the skeleton needs a balanced diet containing both macronutrients (energy, proteins, fats and carbohydrates) and micronutrients (vitamin and minerals) for its normal development and maintenance. The two key nutrients for bone health are the mineral calcium and vitamin D. Calcium is a major structural component of the bone tissue and the skeleton also acts as a reservoir of calcium for maintaining calcium levels in the blood. A large number of dietary components have been proposed as determinants of peak bone mass. The majority of work examining the effect of nutrition on bone has focused on calcium and phosphorous due to them being major constituents of bone tissue. However the trace elements such as zinc, manganese and copper are necessary for growth development and maintenance of healthy bones (Chaudhn Tauseef, 2006)

Dietary components such as magnesium, fluoride, ascorbic acid and vitamin k work biologically at the level of bone itself. Vitamin A, B6 and D are also necessary for healthy bone formation. (Singh, Willet, et al, 2002)

There is clear evidence that adequate vitamin D and calcium intake also play significant roles in ameliorating the severity of osteoporosis and are necessary for optimal response to pharmacologic intervention (Chan, Scott, Sen, 2010). Most clinical guidelines recommend supplementation with calcium and vitamin D to optimize the efficacy of pharmacologic therapies for osteoporosis (Chan, Scott, Sen, 2010)

4.7.1 Calcium

Calcium is essential for various body functions, such as nerve impulse transmission, muscle contraction, and blood clotting. About 99 per cent of calcium is found in the skeletal system but is leeched from the bones when the plasma calcium concentration is low. With low blood levels of calcium, parathyroid hormone is secreted, leading to the synthesis of calcitriol, which results in bone resorption and the release of calcium; if abundant calcium is present in the serum, this cycle will not occur and bone turnover will return to normal levels (Spangler, Phillips, Ross, Moores, 2011)
Over the time even minor negative calcium balance leads to a reduced bone mass. Such negative calcium balance is not detectable by the commonly applied diagnostic test. It is therefore important when investigating patients with reduced bone mineral density that every mechanism possibly contributing to a negative calcium balance is carefully be considered (Deutschmann, Weger, Weger, kotanko, et al, 2002)

A chronically low intake of calcium in the diet decreases bone mass and leads to an increased risk of osteoporosis and bone fracture (Chan, Scott, Sen, 2010)

4.7.2 Vitamin K

Large amounts of vitamin K1 and K2, comparable to quantities contained in liver are found in cortical and trabecular bone compartments. Bone formation by osteoblasts involves post-translational gammacarboxylation of glutamate residues on three bone proteins: osteocalcin, matrix Gla protein, and protein S. Vitamin K is a necessary cofactor

for gammacarboxylation. When gammacarboxylation is lower than normal, the osteocalcin is undercarboxylated (also called “free” osteocalcin) and has a lower affinity for hydroxyapatite than the carboxylated protein. Serum concentrations of undercarboxylated osteocalcin have an inverse correlation with concentrations of vitamin K1, and can be considered a marker of vitamin K status in bone. Vitamin K also decreases bone resorption, in part by inhibiting the activity of prostaglandin H synthase in osteoclasts, with a resulting decrease in the synthesis of prostaglandin E2. It has been found that elderly women with osteoporotic fractures have lower concentrations of serum vitamin K than controls. Serum concentrations of under carboxylated osteocalcin have an inverse correlation with BMD and a positive correlation with hip-fracture risk. Treatment with menatetrenone (menaquinone-4 belongs to the vitamin K2 group) decreased bone loss and increased concentrations of markers of bone formation in hemiplegic patients and in women treated with leuprorelin, and decreased the frequency of fractures in patients with osteoporosis. Some epidemiological data suggest that there is an inverse correlation between the risk of an osteoporotic fracture and consumption of green vegetables containing high amounts of vitamin K1.Warfarin is a competitive inhibitor of vitamin K and decreases gammacarboxylation. Some, studies have shown that BMD is low and risk of osteoporotic fractures high in patients treated with warfarin. Warfarin does not affect the inhibition of bone resorption by vitamin K2, since this inhibition may be mediated by a side chain that warfarin does not compete with.(Veasy L George, 2001)

Low dietary intake of vitamin K found in green leafy vegetables and cheese is associated with low leafy vegetables and cheese is associated with low bone mineral density (BMD) and increased risk of fracture. (Sutcliffe Anne, 2005)

4.7.3 Vitamin D

The role of vitamin D metabolites is primarily to maintain serum calcium and phosphate levels by directly promoting intestinal absorption of these ions as well as by activating bone resorption Failure of the vitamin D endocrine system during growth causes rickets, which is a prominent bone-deforming and sometimes life-threatening disorder. Vitamin D is also important in the maintenance of skeleton integrity in adults. Elderly people tend to have poor dairy calcium and vitamin D intakes, decreased sunlight exposure and dermal production of vitamin D, and diminished production of 1,25(OH)2 D3 with secondary hyperparathyroidism. In turn, vitamin D and calcium supplementation has been demonstrated to significantly increase BMD and decrease the incidence of osteoporotic fractures in the elderly (Rizzoli, Bonjour, Ferrari, 2001)

4.8 Caffeine

High caffeine intake has been associated with decreased BMD in post-menopausal women who have low calcium intakes (Sutcliffe Anne, 2005)
Framingham study found that hip fracture risk was modestly increased with heavy caffeine use, but not for intake equivalent to one cup of coffee per day. ‘’Since caffeine use may be associated with other behaviors that are, themselves, risk factors for fracture, the association may be indirect’’ he says. ‘’Further studies should be performed to confirm these findings.’’(Kiel, et al)

Earlier research seemed to show that caffeine increases the loss of calcium, raising the risk of osteoporosis. Even in a fairly recent study, women aged 65–77 who drank more than 300 milligrams (mg) of caffeine daily and about 18 ounces of regular coffee, showed greater bone loss over a three-year period than those who drank less. But the bone loss occurred only among a minority of women with an unusual variation in their cell vitamin D receptors.

High caffeine consumption only seems to cause bone loss in elderly women who don’t get enough calcium. As long as elderly women get the recommended 1,200 mg of calcium a day, it should be safe for them to drink up to 300 mg caffeine or about 18 ounces

of coffee or its equivalent. Caffeine does not appear to adversely affect the bones of premenopausal women at all (Collins Karen, 2004)

4.9 Smoking

A history of smoking carries a modest but significant risk for future fractures. Current smoking is associated with a significantly increased risk of any kind of fracture in men and women with the effect waning slowly after a person stops smoking (Sutcliffe, 2005)

4.10 Alcohol

Although the influence of modest alcohol intake on the skeleton is uncertain it may affect calcium metabolism and lead to reduced bone density. Heavy alcohol consumption is associated with a reduction in bone density and increased fracture risk. Ethanol may have a direct effect on osteoblasts (Sutcliffe, 2005)

4. 11 Exercise

Physical :activity is important to the skeleton since the associated weight bearing and muscular activity stimulate bone formation and increase bone mass, while immobilization leads to rapid bone loss The positive responses of the skeleton are site specific to the loading pattern and the type of activity also influences the degree of response of the bone loading. The starting age of activity is important with the benefit to bone being doubled if the activity is commenced before or at puberty (Sutcliffe, 2005)

In adulthood, exercise appears to largely preserve bone rather than add new bone and in the immediate post-menopausal years it is unlikely that exercise will balance the effect of oestrogen deficiency. Individually targeted exercises focusing on muscle strength and

balance can improve gait, co-ordination, proprioception and reaction time in older people, decreasing the risk of falls (Sutcliffe, 2005)

4.12 Secondary causes

Among men, 30 per cent to 60 per cent of osteoporosis cases are associated with secondary causes (most commonly hypogo nadism, glucocorticoid use, and alcoholism); among perimenopausal women, more than 50 per cent of cases are associated with secondary causes (most commonly hypoestrogenemia, glucocorticoid use, thyroid hormone excess, and anticonvulsant therapy). The prevalence of secondary conditions is thought to be lower in postmenopausal women, but the actual proportion is unknown. (Mauck, Clarke, 2006; p.662-672)

The cost-effectiveness of testing for secondary causes of osteoporosis is unknown because cost-effectiveness analyses have yet to be performed. In a chart review study, Tannenbaum et al examined this issue in perimenopausal and postmenopausal women found that a testing strategy consisting of 24-hour urinary calcium, serum calcium, and serum parathyroid hormone determinations in all women and serum thyrotropin measurements in women receiving thyroid replacement therapy would be sufficient to diagnose secondary causes of osteoporosis in 86 percent of women adding 25-hydroxyvitamin D would diagnose secondary causes in up to 98 per cent. However, this study was observational and small. (Mauck, Clarke, 2006; p.662-672)

Jamal et al reported that the prevalence of abnormal test results in postmenopausal women with and without osteoporosis was similar, with the exception of low thyrotropin. These authors concluded that routine laboratory testing (other than thyrotropin measurements) in otherwise healthy women with osteoporosis was not useful. Clearly, more research is needed in this area, especially in premenopausal and perimenopausal women and in men because the prevalence of secondary causes of osteoporosis in these groups is high (Mauck, Clarke, 2006; p.662-672)

There are a number of clinical disorders that affect bone density and osteoporosis risk. This diverse group includes endocrine abnormalities, adverse effects of medications,

immobilization, and disorders of the gastrointestinal tract, renal disease and cancer. It is difficult to ascertain the true incidence of secondary osteoporosis but several studies have estimated that it may occur in 20 to 30 per cent of post-menopausal women and in more than 50 per cent of men with osteoporosis (Sutcliffe, 2005)

EVALUATION

Patients at risk for osteoporosis and related fractures should receive BMD testing by central DEXA. These patients include women age 65 years or older (regardless of risk factors), postmenopausal women under age 65 years with risk factors and postmenopausal women with a history of nontraumatic fracture. In addition, testing should be considered for men age 70 years or older, for patients with diseases that may result in decreased bone strength, for patients taking long-term medications known to decrease BMD, and to assess response in patients receiving medications for the treatment of osteoporosis (Mac Laughlin, Raehl, 2008)

5. PREVENTION AND TREATMENT

In order to be able to identify patients at risk of fractures and optimize pharmacotherapy, a thorough risk factor analysis is recommended. Two major areas of risk factor assessment that should be considered, particularly for older individuals, include an assessment of both “bone” and “non-bone” related risks. “Bone-related” risk factors are those factors associated with bone density. “Non-bone” risk factors are variables associated with fracture risk unrelated to bone density, and may increase fracture risk irrespective of osteoporosis diagnosis. However they compound the risk of an osteoporosis end-point in a patient who has decreased bone density. (Mc Laughlin, et al 2006)

Age is not a drawback to start osteoporosis prevention strategies. Healthcare profession also have to educate themselves in order to assess and counsel their clients on the risk factors, nutrition recommendations, physical activities needs and pharmacological options as well as other life styles modifications required to obtaining and maintaining optimum bone density and health. The ones already diagnosed with osteoporosis can also benefit from employing the same assessment and educational principles to reduce or halt further bone loss

There are now a number of treatments for osteoporosis that increase bone density and reduce the incidence of fractures. These drugs can be divided into anti-resorptive agents that inhibit osteoclast activity and anabolic agents that increase bone formation. Anti-resorptive treatments include bisphosphonates, raloxifcne. Caicitonin, hormone replacement therapy (HRT) and vitamin D and calcium supplements. Teriparatide acts in an anabolic way and strontium ranelate is the first in a new class of drugs, dual acting bone agents (DABAs), that increase bone formation and reduces bone resorption (Sutcliffe, 2005**)**

5.1 Non pharmacologic treatment

Several non pharmacologic interventions for the prevention of osteoporotic fractures should be considered for all patients. The attainment of high peak bone mass early in life is one of the most important protective factors against reduced BMD later in life. In addition, strategies to maintain current bone mass for patients in later stages of life should be instituted. Appropriate weight bearing exercise, minimization or elimination of various modifiable risk factors (example; smoking, excessive alcohol intake, maintenance of euthyroid status), and maintenance of adequate calcium and vitamin D intake should be recommended for all patients. (Mac Laughlin, Raehl, 2008)

5.2 Pharmacological treatment

Pharmacological goals for osteoporosis include halting bone loss, improvement of BMD, and reduction in fragility fractures. However, drug therapies that have been shown to decrease fractures, particularly at the hip, should be used as hip fractures have the greatest impact from a patient and societal perspective. Pharmacological therapies for prevention of fractures in patients with osteoporosis include antiresorptive therapies such as the bisphosphonates (alendronate, ibandronate, risedronate) and selective oestrogen receptor modulator raloxifene and the anabolic agent teriparatide.

Pharmacological treatments for osteoporosis can be broadly divided according to their mode of action. The majority of the agents act by slowing bone resorption, thereby preventing the relentless bone loss underlying the disease

Pharmacological treatment of osteoporosis is conducted in accordance with the principles of evidence-based medicine, which incorporates information derived from the highest- quality investigations with clinical judgment and patient values to allow optimal clinical management. The important points in the choice of drugs are the preventive effects on vertebral, non-vertebral, and hip fractures, the consistency of the results of randomized, controlled trials, and long-term efficacy and safety. Meta analyses have demonstrated the reliable efficacy of several anti-resorptive agents for preventing vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis alendronate, risedronate, and raloxifene are efficacious agents for preventing vertebral fractures in postmenopausal women with osteoporosis. Alendronate and risedronate have also been shown to be especially efficacious for the prevention of non-vertebral fractures and hip fractures (Jun Iwamoto, 2008 et al)
Antiresorptive therapies reduce osteoporotic fracture risk by increasing bone mass density and suppressing bone remodeling (Boonen, Vanderschueren, et al 2006)

Treatments for osteoporosis are not the same as the way they are diagnosed, although some experts have recommended that they should be. In the United States, most experts

agree on the treatments outlined by the World Health Organization, which recommends that the given individuals be considered for pharmacological.

The most commonly used osteoporosis treatments in Europe are currently the selective estrogen receptor modulator (SERM) raloxifene; the bisphosphonates alendronate, risedronate, ibandronate and zoledronic acid; agents derived from parathyroid hormone (PTH); and strontium ranelate (Reginster, 2011)

Bisphosphonates are compounds that bind avidly to hydroxyapatite crystals on bone surfaces and are potent inhibitors of bone resorption. Through inhibition of osteoclastic activity, they reduce bone remodelling, improve bone mineral density and are associated with reduced rates of fracture among women and men, although less well documented in the latter group. Alendronate (70 mg once weekly) and risedronate (typically 35 mg once weekly) are the most commonly used bisphosphonates worldwide. The most important benefit of bisphosphonates lies in the prevention of vertebral, nonvertebral and hip fractures in people who low bone mineral density (T score −2.5 or lower) or prevalent fractures, or both (Rahmani, Morin, 2009)

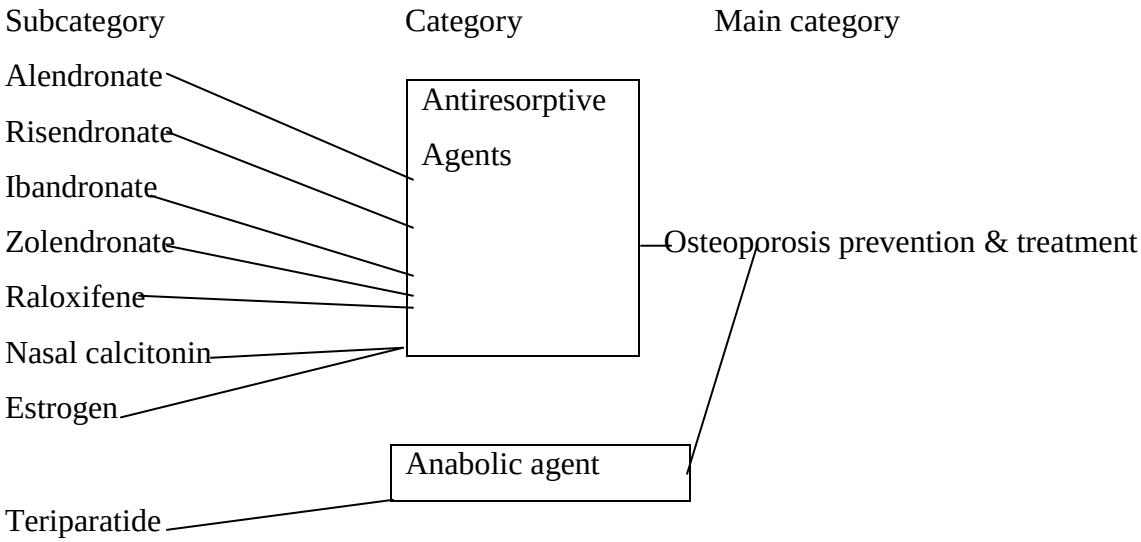
According to results of large randomized, controlled trials, bisphosphates, raloxifene, calcitonin, parathyroid hormone and strontium ranelate effectively prevent fractures in postmenopausal women with osteoporosis.

Low energy fragility fractures have been suggested as a result of complication of long-term bisphosphonate therapy due to over suppression of bone turn over though bisphosphonates are widely used in practice, many questions still remain regarding the appropriate duration of use. Very few studies have evaluated the efficacy and safety of these medications beyond 5 years of therapy. (Shcmidt, Eltorner, et al 2010)

The primary goal of pharmacological therapy in patients with osteoporosis is to reduce the risk of future fracture, not just increase bone density. Currently, the pharmacological agents available for treatment of osteoporosis fall into 1 of 2 categories: antiresorptive agents or anabolic agents. All the currently available drugs except teriparatide are antiresorptive agents (figure 1). These agents reduce bone resorption more than promote bone formation and thereby suppress bone turnover and loss, whereas anabolic agents stimulate bone formation more than reduce bone resorption (Mac Laughlin, Raehl, 2008)

The figure below shows osteoporosis medications as they have been classified to their different classes of agents.

Figure 1. Treatments of osteoporosis approved by Food and Drug Administration



Anabolic therapies stimulate bone formation, repairing defects at a micro architectural level leading to a substantial increase in BMD in the presence of adequate calcium and vitamin D status. A high proportion of patients with osteoporosis are at significant risk of calcium and vitamin D insufficiencies unless they receive supplementation. Anabolic agents may provide significant benefits to patients with severe osteoporosis (especially patients with previous osteoporosis-related fractures), as well as patients who have not tolerated or have had inadequate responses to antiresorptive therapy

Therapeutic decisions should be based on a balance between benefits and risks of treatment, which must be carefully considered in each particular case both by the physician and the patients, no single agent is appropriate for all patients and, therefore, treatment decisions should be made on an individual basis, taking into account all measures of treatment effect and risk before making informed judgments about the best individual treatment option. (Reginster, 2011)

All clinical trials of antiresorptive and anabolic therapies should be carried out in individuals who have good calcium and vitamin D status. Experts recommend that patients

receiving antiresorptive and anabolic treatment for osteoporosis must have adequate calcium intake and optimal vitamin D to maximize benefits.

5.2.1. Calcium

Adequate calcium intake has been demonstrated to be significant for increasing and maintaining bone mass (Dontas, Yiannakopoulos, 2007)
Evidence suggests that calcium intake is important during skeletal growth and peak bone mass development and there is a consensus that calcium supplementation may be effective in reducing bone loss in late post-menopausal women, particularly m those with low habitual dietary calcium intake (Sutcliffe, 2005)
Calcium is the fifth most abundant mineral in the human body accounting for 1-2 per-cent of adult body weight. Over 99 per cent of total body, calcium is found in the inor-ganic phase of bones and teeth. It is absorbed depending on its interaction with other dietary constituents and physiological factors such as calcium regulating parathrormone requirements if optimal bone development is to be achieved. (Chaudhn, 2006)

Due to a decrease in estrogen production after menopause, women's bodies are less able to retain calcium from dietary sources. Calcium supplementation has been used for decades to prevent this calcium depletion, maintain bone mass, and prevent and treat osteoporosis (Spangler, Phillips, Ross, Moores, 2011)

5.2.1.1 Calcium and bone health

Healthy bones provide a strong foundation, allowing mobility and protection from in-jury. They also serve as a bank for important minerals, such as calcium, that help sup-port numerous organs in our body. Developing healthy bones begins at birth and proceeds throughout life. The human body uses calcium to build healthy bones until about 30 years of age. After the mid-30's, bone loss slowly begins to occur. Women lose bone quickly after menopause. Importantly, healthy habits can help to limit the bone loss that occurs. (Carmona, 2004)

5.2.1.2 Calcium absorption and excretion

Dietary calcium absorption in adults with the usual intake is approximately 25 per cent to 35 per cent. Calcium absorption is dependent on several factors including age, vitamin D and exposure of food to gastric acid. (Chaudhn, 2006)

Decreased calcium absorption occurs during menopause and maturity. When vitamin D is insufficient, calcium absorption is also decreased when the gastric acidity is low in the presence of liver, pancreatic, small bowel disease and mental and physical stress (Chaudhn, 2006)

Elderly women have an impaired intestinal response to 1, 25 (OH). This defect may contribute to the negative calcium balance, secondary hyperparathyroidism and bone loss in aging women (Chaudhn, 2006)

The bone calcium content is the result of whole body calcium balance which is determined by uptake in the gut and faecal and renal calcium excretion (Deutschmann, Weger, kotanko, et al 2002)

5.2.1.3. Calcium supplementation

Calcium supplementation alone has been demonstrated to increase bone mineral density and to decrease the rate of fracture in post menopausal women (Chan, Scott, Sen, 2010)
Calcium supplementation may prevent bone loss or even mildly increase BMD and some data suggest that it may minimally reduce fracture risk.
For patients with osteoporosis, calcium supplementation should be used as an adjunct to other pharmacological interventions rather than as monotherapy. The National Institutes of Health consensus conference guidelines suggest that women should optimize their elemental calcium intake to 1000 mg/d until menopause and increase it to 1500 mg/d thereafter. Men should optimize their elemental calcium intake to 1000 mg/d until age 65, and then increase it to 1500 mg/d. (Mauck, Clarke 2006; p.662-672)
Most experts recommend obtaining as much calcium as possible from foods because calcium in foods is accompanied by other nutrients that assist the body in utilizing calcium (Chaudhn 2006)

The present recommended minimum daily calcium intake for adults ranges from 1000-1300 mg. Even though calcium is relatively common in the diet, supplementation is frequently necessary. Intake is often insufficient due to religious or dietary restrictions, lactose intolerance. It is recommended that if dietary intake of calcium-rich foods is inadequate, supplements containing elemental calcium (calcium citrate and calcium carbonate) should be taken. It should be noted that commonly used multivitamin supplements often do not contain sufficient calcium to make up for deficiency in the diet. Increasing calcium intake alone is insufficient for adequate maintenance of bone mass (Siew Pheng, et al 2010)

5.2.2 Vitamin D

Vitamin D is unique because it can be obtained both through skin exposure to sunlight and through food or supplements. Like all the other vitamins and minerals, calcium is available only through food or supplements although calcium and vitamin D foods are the preferred source of dietary. Several organizations suggest that older people may need supplements to meet their high needs for these nutrients. (Cheng, Johnson, Lewis, et al 2003)

Vitamin D is necessary for optimal absorption of calcium and in housebound older people. Vitamin D deficiency contributes to osteoporosis and fractures through its effects on bone fragility and impaired muscle strength sunlight exposure, as a result of strict dress codes where most of the body is covered, may expose certain ethnic races to the risk of vitamin D deficiency. The benefit of a high consumption of fruit and vegetables and the resulting high intake of dietary alkali on skeletal integrity bas been emphasized (Sutcliffe, 2005)

Addition of supplemental vitamin D to the diet has also been shown to reduce fracture rate in postmenopausal women (Chan, Scott, Sen, 2010) Vitamin D supplementation, particularly with the active form (calcitriol) may be theoretically important for frailer, institutionalized individuals or those with chronic health conditions (PTH disorders, chronic renal failure, and dialysis) due to the inability or reduced capacity to convert vitamin D to the active form. Vitamin D is an essential component that, along with parathyroid hormone (PTH), regulates serum calcium concentrations. Inadequate vitamin D intake may be a greater concern than poor calcium intake, as vitamin D may not be as

prevalent in the diet as calcium, and patients may be less aware of vitamin D requirements than calcium. Low exposure to sunlight and poor renal function may also lead to decreased concentrations. Yet supplemental vitamin D, with or without calcium, has been shown to reduce fracture rates and may also have effects on muscle strength and risk of falling (Mac Laughlin, Raehl, 2008).

Adequate intake of both calcium and vitamin D are an essential part of osteoporosis prevention, and no treatment regimen should be considered complete without these adjunctive therapies. There are numerous studies that have reported outcomes of supplemental calcium, vitamin D. Adequate calcium and vitamin D intake is considered an essential component of osteoporosis prevention and treatment, yet many men and women over age 65 years consume only 600 mg of calcium daily. However, there is controversy regarding calcium and vitamin D supplementation. There is no universal consensus for the most appropriate daily dose though all groups recommend at least 1000 mg, and data are lacking regarding the most effective calcium salt. In addition, questions have been raised about the efficacy of calcium and vitamin D for prevention of fractures. (Mac Laughlin, Raehl, 2008)

In addition to its structural role, bone serves as the body's nutrient reserve of calcium. Ingested calcium is absorbed from the intestine in two ways: passively and by vitamin D-mediated active transport, both of which become less efficient with age. The efficiency of calcium absorption decreases further in the presence of vitamin D insufficiency. Vitamin D status is generally determined by measuring the serum concentration of the major circulating form of vitamin D, hydroxyvitamin D [25(OH) D]. As people age, the skin's capability to synthesize vitamin D decline, intestinal vitamin D absorption also becomes less efficient. These changes may be compounded by lower exposure to the sun, as a result of diminished physical activity, and reduced dietary vitamin D intake; people who live at northern latitudes or who are housebound or living in an institution are at particular risk of vitamin D insufficiency . Adequate dietary calcium intake is critical in maintaining bone mass, whilst vitamin D plays a key role in modulating calcium homeostasis and maintaining muscular strength. There is therefore a strong rationale for giving both calcium and vitamin D supplements to prevent and treat osteoporosis (Boonen, Vanderschueren, et al 2006)

After synthesis in the skin or ingestion through the diet, vitamin D3 is stored in the liver, adipose tissue and muscle, where it has a half-life of about 60 days. It is converted into 25- hydroxyvitamin D3 in the hepatocytes. The serum concentration of 25-hydroxyvitamin D3 is the best indicator of the nutritional and functional status of vitamin D. Although circulating calcitriol (25-dihydroxyvitamin D3 or 1,25- dihydroxy cholecalciferol) is the vitamin D hormone regulating intestinal calcium and phosphate absorption, it is not an appropriate indicator of clinical vitamin D status in most cases (Hanley, Cranney, et al 2010). The few foods that naturally contain vitamin D for example certain fish are not consumed regularly. Consequently, Canadians depend on fortified dietary sources or supplements to maintain adequate vitamin D status cases (Hanley, Cranney, et al 2010).

The preferred source of calcium is foods such as dairy products. Some dietary sources of calcium include yogurt (400 mg per cup), milk (300 mg per cup), calcium-enriched orange juice (300 mg per cup), cheese (150-180 mg/oz), and canned salmon with bones (180 mg per 3 oz). Calcium supplements are an alternative means by which optimal calcium intake can be reached in those who cannot meet this need by diet alone. Numerous calcium supplements are available in a variety of salts that can be used to supplement dietary calcium intake. The most commonly used calcium supplements are calcium carbonate or calcium citrate. Factors to consider in selecting an agent include absorption, convenience, and cost. Calcium absorption is generally maximal at individual doses of 500 mg of elemental calcium. Calcium carbonate contains 40 per cent elemental calcium, requires stomach acid for digestion and absorption, and is the least expensive option. It should be taken with meals in doses of no more than 500 mg of elemental calcium at a time. Calcium citrate contains 21per cent elemental calcium, does not require stomach acid for digestion, and is more available but is more expensive than calcium carbonate. Calcium citrate can be taken with or without food in doses of no more than 500 mg of elemental calcium at a time. Calcium citrate is the preferred calcium supplement for patients who are hypochlorhydric or achlorhydric (including those taking gastric acid–inhibiting drugs) and for patients with a history of kidney stones. The most common adverse effects of all calcium supplements are constipation, bloating, and gas; however, these adverse effects may be less frequent with calcium citrate. Patients taking medications whose absorption may be impaired by calcium (levothyroxine, fluoroquino-

lones, and angiotensin-converting enzyme inhibitors) should also be advised to avoid taking calcium supplements within several hours of taking these medications. Vitamin D supplementation may prevent bone loss or mildly increase BMD and modestly reduces vertebral and non vertebral fracture risk in vitamin D–deficient individuals. (MacLaughlin, Raehl, 2008)

5.2.3. Bisphosphonates (Alendronate, Risendronate, Ibandronate, Zolendronate)

Some treatments developed for post menopausal osteoporosis have also been registered for the prevention and treatment of corticosteroid-induced osteoporosis and presently bisphosphonates are the treatment of choice for this indication.(Cremers, Garnero, 2006)

As far as medical treatment is concerned, the use of bisphosphonates constitutes a safe and effective therapeutic intervention for the treatment of osteoporosis.. (Brito, Battistella, 2005)

Bisphosphonates are powerful inhibitors of bone resorption. These agents are increasingly used alongside anticancer treatments to prevent skeletal complications and relieve bone pain they are also safe and effective treatment for induced bone loss.
The bisphosphonates are stable analogues of pyrophosphate, but contain a carbon in the backbone of the molecule instead of oxygen. They have a strong affinity for bone hydroxyapatite. Oral bisphosphonates are poorly absorbed, hence the requirement for them to be taken on an empty stomach, with no food or drink for the next 30 minutes. Once absorbed, they rapidly localize to the skeleton, where they inhibit bone résorption by reducing recruitment and activity of osteoclasts and increasing osteoclast apoptosis. The bisphosphonates principally act by prevention of further bone loss and are associated with moderate increases in BMD (Reginster, Akesson et al, 2011)
In all published clinical trials, calcium and vitamin D supplements have also been used with the bisphosphonates as adjunctive therapy. In the RECORD study, concentrations of 25 (OH) , vitamin D were measured only in a very small subset of the patients. The vitamin D status of the majority of participants was unknown. Low serum concentrations of vitamin D are widespread in the U.K and moderate vitamin deficiency in older

people results in poor bone and muscle strength. Serum 25 (OH) vitamin D concentrations that correlate with clinically significant effects on muscle function and fracture prevention is at least 70 nmol/L It is uncertain whether intake of Calcium/ vitamin D supplements has any increased benefits on the patients taking bisphosphonates.

One recent meta-analysis evaluated the impact of vitamin D status on changes in bone mineral density in firstly patients with post menopausal osteoporosis bisphosphonates and secondly following discontinuation of bisphosphonates after a long term use, two patient groups were recruited. The first study population comprised of 112 women treated with a bisphosphonate. The second study population consisted of 35 women who had been on bisphosphonates for more than 5 years in whom the treatment agent was discontinued. Baseline BMD, changes in BMD following treatment, duration of treatment, serum 25 (OH), vitamin D, parathyroid hormone (PTH), urine C-terminal telopeptides of type 1 collagen (CTX) were obtained on the study participants. In the first study group, subjects with serum vitamin D concentrations (> 70 nmol/L) had a significantly lower serum PTH level (mean [SEM] 41 ng/L). PTH concentrations of 41 ng/L or less was associated with a significantly higher increase in BMD at the hip following treatment with bisphosphonates compared to patients with PTH > 41 ng/L (2.5% [0.9] v/s -0.2% [0.9], P = 0.04). In the second study group discontinuation of bisphosphonate for 15 months after long-term treatment did not result in significant bone loss at the lumbar spine and total hip, although a trend towards gradual decline in BMD at the femoral neck was observed. The data suggest that optimal serum 25 (OH) vitamin D concentrations may lead to further reduction in bone loss at the hip in patients on bisphosphonates.

On the other hand, in order that patients with documented osteoporosis derive the expected clinical benefits from antiresorptive or anabolic therapy, calcium and vitamin D supplementation should be given throughout treatment with these therapies. (Boonen, et al 2006)

The long-term bone safety of bisphosphonates has recently been questioned. Unusual fractures and delayed healing, possibly due to over suppression of bone turnover, have been reported In a large longitudinal cohort study of women conducted to determine the effect of dosing frequency on bisphosphonate medication adherence**,** Of 211,319 study

patients, 177,552 (84 per cent) were taking weekly bisphosphonates vs. 33,767 (16 per cent) taking the daily prescription. Although significantly more patients taking the weekly compared with the daily bisphosphonates had adequate medication adherence, only about one third of patients in the daily dosing group and less than one half in the weekly dosing group achieved adequate adherence. Patients new to bisphosphonates had the worst medication adherence over the year (25.2 per cent for weekly vs 13.2 per cent for daily dosing; P<.001). The highest proportion of adequately adherent patients was among those continuing to take their existing weekly bisphosphonates; however, even in this group, only about 48% exhibited adequate medication adherence. (Recker, et al 2005)

5.2.3.1 Alendronate

Alendronate (alendronic acid) is a nitrogen-containing bisphosphonate which binds to bone surfaces and inhibits bone resorption by osteoclasts. Oral alendronate 5 or 10 mg/day produces sustained increases in bone mineral density (BMD) in postmenopausal women with or without osteoporosis, in men with primary osteoporosis and in both men and women with or without osteoporosis receiving systemic corticosteroid therapy. Histomorphometric analyses have found that alendronate does not appear to impair bone quality. Alendronate reduced the risk of radiographic vertebral fracture, clinical vertebral fracture or hip fracture by 47 to 56 per cent in postmenopausal women who had ≥1 existing vertebral fracture and in those with no existing vertebral fractures but who had osteoporosis. In a number of comparative trials in postmenopausal women with osteoporosis, alendronate 10 mg/day was found to be more effective at inducing sustained increases in BMD than intranasal calcitonin than and at least as effective as conjugated estrogens and raloxifene. Alendronate 70mg administered once weekly and 35mg twice weekly are as effective at increasing BMD as 10 mg/day in the patient group. Absorption and disposition of alendronate over the dosage range 5 to 80mg are linear. Beverages (other than water), food and calcium supplements all reduce absorption of alendronate. The drug is either excreted by the kidneys, the only route of elimination, or taken up and sequestered by bone, from where it is slowly released. The mean steady-state volume of distribution of alendronate, excluding bone, is estimated to be at least 28L. The renal clearance rate of the drug is 4.26 L/h and alendronate is not metabolized.

Excretion involves multiple phases that are initially rapid, then become very slow as alendronate is released from bone. The estimated mean terminal elimination half-life of alendronate is 10.5 years. (Sharpe, et al 2001)

In clinical trials, alendronate was generally well tolerated when taken as recommended. The drug has been associated with upper GI tract adverse events, although the extent to which alendronate is responsible for these events has not been clearly established. Alendronate should be considered a treatment of choice in postmenopausal women with osteoporosis. Alendronate is also a suitable treatment option for primary osteoporosis in men and for corticosteroid-induced osteoporosis in both men and women. (Sharpe, et al 2001)

A prospective, randomized controlled trial, in a university based study of 6 months duration. 1000 mg of calcium plus 10mg of alendronate daily significantly increased in nine densitometric parameters in the experimental group, although statistical significance was attained in only two of those parameters compared to the control group who received only 1000 mg of calcium that was observed with an increase of only one parameter whereas the remaining 11 presented either no alteration or a decrease Comparison of variations in mean UE BMD showed that there was a consistent increase in bone density in patients treated with alendronate plus calcium (0.03), whereas control group patients presented greater variability in UE BMD values, which were higher in some and lower in others (mean, _0.03). Mean increase in UE BMD in the experimental group was greater than in the control group in a marginally significant manner ($P<0.14$). No significant difference between the two groups was found in the BMD variation at the trunk ($P<0.54$). The author concluded that the use of alendronate had a positive effect on bone mineral density in SCI patients and therefore represents a potential tool for prevention and treatment of osteoporosis in this population. (Brito, Battistella, 2005).

The effects of alendronate on markers of bone turnover in postmenopausal women with osteoporosis have been compared with those of a number of other treatments alone and in combination with alendronate. In another clinical trial, continuous oral alendronate 10 mg/day significantly reduced levels of serum markers of bone formation and urinary markers of bone resorption compared with placebo for at least 7 years in postmenopausal women with osteoporosis. Alendronate had similar effects on bone turnover markers

in men with primary osteoporosis or osteoporosis associated with low serum testosterone levels, both men and women with corticosteroid-induced osteoporosis and postmenopausal women without osteoporosis. (Sharpe, et al 2001).

Findings from randomized, controlled, head-to-head trials show that women who received alendronate have greater gains in bone mineral density and greater reductions in bone turnover markers within 12 and 24 months of initiation than those who received risedronate or raloxifene. Although bone mineral density is a strong predictor of fracture, differences in these surrogate markers may not translate into appreciable differences in fracture risk (Suzanne M. Cadarette et al 2008). Alendronate 5mg/day is effective in increasing vertebral BMD and stabilizing BMD at the femoral neck for at least 5 years in postmenopausal women without osteoporosis, although it does not appear to be as effective in increasing BMD in this patient group as some HRT regimens. The drug increases BMD in postmenopausal Asian women as effectively as in postmenopausal Caucasian women. There is evidence from FIT that alendronate 5 mg/day for 2 years followed by 10 mg/day for 1 to 2 years significantly lowers vertebral fracture incidence in postmenopausal women with low BMD but without osteoporosis. The recommended dosing instructions for alendronate 10 mg/day may be inconvenient for some patients on a daily basis. For these people, once weekly alendronate administration might be a more convenient option. Alternative dosing regimens of 70mg once weekly and 35mg twice weekly were as effective as 10 mg/day at increasing BMD and had no clear advantage or disadvantage in tolerability in a clinical trial (Sharpe, et al 2001)

5.2.3.2 Risedronate

Risedronate is a pyridinyl bisphosphonate that has been shown to be effective in the prevention and treatment of osteoporosis at a daily dose of 5 mg, a once-a-week dose of 35 mg, a dose of 75 mg on 2 consecutive days a month, or a once-a-month dose of 150 mg. Treatment with risedronate for 36 months reduced the risk of vertebral fractures by 41 per cent and non vertebral fractures by 39 per cent relative to placebo in women with at least one existing vertebral fracture17 and the risk of hip fractures by 40 per cent relative to placebo in women aged 70 to 79 with osteoporosis. Retrospective analyses showed that risedronate significantly reduced the incidence of nonvertebral and clinical vertebral fractures within 6 months. (Boonen, et al 2010).

Given the aging population and the predicted increases in the incidence of osteoporosis and related fractures, information on the relationships between aging and fracture incidence and the effect of treatment on fracture risk as the population ages would be of interest. The large database developed during the risedronate clinical trial program provides the opportunity to explore these relationships further in a large population of postmenopausal women with osteoporosis. The effect of age on fracture risk is frequently examined by holding other risk factors, such as bone mineral density (BMD), constant, although because other risk factors change as patients' age, this approach may not be optimal. Using pooled information from several risedronate, analyses were conducted to quantify the effect of age on fracture risk and the benefit of risedronate treatment for different age groups without adjusting for BMD. Prediction of fracture risk in different age groups provides information that clinicians and patients need as they weigh treatment and lifestyle options. Results from observational studies suggest that risedronate may reduce the risk for nonvertebral fracture (clavicle, hip, humerus, leg, pelvis, and wrist) within 12 months more effectively than alendronate or nasal calcitonin (Cadarette, et al, 2008)

5.2.3.3 Zoledronic acid

This is the most potent bisphosphonate, zoledronic acid, which is administered once yearly as an intravenous infusion, has been developed to overcome the limited gastrointestinal absorption and poor patient adherence associated with oral bisphosphonates. Zoledronic acid has also been found to increase BMD in a similar manner when given as an intermittent i.v. infusion. In August 2007, zoledronic acid became the first bisphosphonate to receive FDA approved labeling for once-yearly administration in the treatment of osteoporosis in postmenopausal women (Reginster, 2011) .

2 large clinical trials that compared yearly infusion of 5 mg of zoledronic acid with placebo: one involved postmenopausal women at high risk of fractures have been identified. The HORIZON trial included 7765 postmenopausal women aged 65-89 years with BMD T-scores of -2.5 SD or lower at the femoral neck, with or without evidence of existing vertebral fracture, or a T-score of-1.5 SD or lower with evidence of >2 mild or >1 moderate vertebral fractures, just under two-thirds of women had baseline fractures. Pa-

tients were randomized to receive a 15-minute, 5 mg infusion of zoledronic acid (n = 3889) or placebo (n = 3876) at baseline, 12 months and 24 months; follow-up continued to 3 years. The primary endpoints were new vertebral fracture in patients not taking concomitant osteoporosis medications and hip fracture in all patients. The relative risk of vertebral fracture with zoledronic acid was 0.30 (95% CI 0.24, 0.38). New vertebral fractures occurred in 3 percent of women in the zoledronic acid group and in 11% of women in the placebo group. In the HORIZON trial, the hazard ratio for hip fracture with zoledronic acid was 0.59 (95% CI 0.42, 0.83). At 3 years, the incidence of hip fracture was 1 percent (52 women) in the zoledronic acid group and 3 per cent (88 women) in the placebo group. The incidence of any clinical fracture, clinical vertebral, or non-vertebral fracture in postmenopausal women aged 75 and older was significantly lower in the ZOL group than in the placebo group over 3 years (P<.001, P<.001, and P=.002, respectively). A similar finding has been shown for any clinical fracture and clinical vertebral fractures at 1 year (P=.03 and P=.009, respectively), but the incidence of non-vertebral fracture at 1 year and hip fracture at 1 and 3 years was lower for the ZOL group although not significantly (Black, et al,2007)

In another trial that involved men and women with a recent hip fracture. Zoledronic acid was also found to decrease mortality by 28 percent compared with placebo in the study involving patients with a recent hip fracture (number needed to treat = 29). The use of zoledronic acid was associated with a risk reduction in vertebral fractures (RR 0.30, 95% CI 0.24–0.38; number needed to treat = 14) and nonvertebral fractures (RR 0.75, 95% CI 0.64– 0.87; number needed to treat = 38). (Lyles, et al. 2007)

5.2.3.4 Ibandronate

It is a nitrogen-containing bisphosphonate available in once-monthly oral and quarterly intravenous formulations for intermittent administration, has been approved for the treatment of osteoporosis in postmenopausal women in the EU, the US and many other countries worldwide. The once-monthly oral formulation has also been approved for the prevention of postmenopausal osteoporosis in the US. Ibandronate is an effective and generally well tolerated bisphosphonate that offers an alternative to other bisphosphonates as a first-line treatment for postmenopausal osteoporosis. It occupies a similar po-

sition with respect to the prevention of osteoporosis in postmenopausal women at risk for the disease. The once-monthly oral and quarterly intravenous dosage regimens have the potential to improve treatment adherence and persistence, and hence clinical outcomes, compared with more frequently administered oral bisphosphonates. Intravenous ibandronate may be particularly useful for postmenopausal osteoporotic women who are noncompliant with, or are unable to tolerate or receive, oral bisphosphonates. Intermittent ibandronate extends the range of pharmacological therapies for the treatment and prevention of postmenopausal osteoporosis it inhibits osteoclast-mediated bone resorption. In clinical trials in postmenopausal women with osteoporosis, approved oral and intravenous ibandronate dosage regimens reduced bone turnover, and increased lumbar spine and proximal femur bone mineral density (BMD) and mechanical strength. Bone newly formed in the presence of ibandronate is normal in terms of quality and mineralization. Absorption of oral ibandronate, although rapid, is low (bioavailability 0.63%) and markedly impaired by food and beverages (other than plain water). After initial systemic exposure, ibandronate is either sequestered in bone (≈40–50% of the circulating dose in postmenopausal women) or excreted in the urine (renal clearance of the drug is linearly related to creatinine clearance). Ibandronate only moderately bound to plasma proteins and does not undergo hepatic metabolism; hence, it has a low potential for displacement from plasma proteins and metabolic drug-drug interactions with other medications. (Frampton, Perry, 2008).

Subsequent clinical studies have provided further evidence of the positive effects of extended-interval ibandronate administration in reducing the risk of vertebral fractures through increasing bone mineral density and reducing bone turnover without compromising bone quality. (Chesnut, 2006).

Ibadronate is approved for the treatment of osteoporosis in postmenopausal women in the EU and the US. Currently, it is the only bisphosphonate available in both oral and injectable forms. The recommended available dosage regimens are 150 mg orally once monthly and 3 mg intravenously (injected over a period of 15-30 seconds) every 3 months. The once monthly oral formulation of ibandronate is approved for the prevention of osteoporosis in the postmenopausal women in the US. The once daily oral formulation of ibandronate is not commercially available. Patients prescribed once

monthly oral ibandronate should take their tablet preferably on the same date each month and after an overnight fast (6 hours or more) and /or 1 hour or more before the first food and drink of the day or any other oral medication or supplement. The tablet should be taken with plain water while sitting or standing in an upright position and patients should not lie down for 1 hour afterwards. (Frampton, Perry, 2008).

5.2.4 Other treatments

5.2.4.1 Raloxifene

Is a selective estrogen-receptor modulator, has estrogenic activity in some tissues for example bone and antagonist for effects in others example breast. Daily use of raloxifene (60 mg/d) increases bone mineral density and has been shown to diminish the risk of estrogen-receptor–positive invasive breast cancer by 55% to 90%. (Rahmani, Morin, 2009). Raloxifene selectively interacts with estrogen receptors, exerting an estrogen agonist effect in some areas (bone and lipid metabolism) while acting as an estrogen antagonist in others (breast and uterus). Raloxifene is contraindicated in patients with a history of venous thromboembolic events and should not be recommended for premenopausal women or women concurrently using estrogen replacement therapy. (Karen F. Mauck and Bartl Clarke 2006). Raloxifene was the first SERM approved for the prevention and treatment of osteoporosis in postmenopausal women The MORE study recruited 7705 women aged 31-80 years, at least 2 years postmenopausal with osteoporosis defined as low BMD or radio graphically apparent vertebral fractures. Prior to randomization, patients were stratified to one of two study groups at the time of radiography screening: 5064 were assigned to study group 1 if they had no vertebral fractures but a femoral neck or lumbar spine BMD T-score of >2.5 SD; and 2641 were assigned to study group 2 if they had vertebral fractures. Within each sub study, women were randomly assigned to treatment with raloxifene 60 or 120 mg/day or placebo for 3 years. Only the results for the 60 mg/day dose were presented, because this is the currently marketed dose in Europe. The relative risk of vertebral fracture with raloxifene was 0.70 (95% CI 0.6, 0.9). New vertebral fractures occurred in 113 (15%) women in the raloxifene group and in 163 (21%) women in the placebo group. These results gave RRR of 30%, an ARR of 7 per cent and an NNT of 16 for vertebral fracture over 3

years. The clinical efficacy of raloxifene against hip fractures over 3 years has not been investigated in a pivotal phase iii study (Reginster, 2011) In a meta-analysis of 7 trials in which postmenopausal women were given raloxifene or placebo, raloxifene was associated with a risk reduction in vertebral fractures (RR 0.60, 95% CI 0.50–0.70; number needed to treat = 2381 to 99 across the range of fracture risk for 2 years of treatment).There was little effect of raloxifene on the risk of other fractures. The RUTH (Raloxifene Use for The Heart) study, involving postmenopausal women at high risk of cardiovascular disease, showed that raloxifene had no effect on the risk of cardiovascular death, coronary artery disease or stroke. Raloxifene, like estrogen, is associated with an increased risk of venous thromboembolism (OR 2.08, 95% CI 1.47–3.02).In practice, raloxifene is generally well tolerated, with transient occurrence of hot flashes and leg cramps in less than 10% of patients. (Cranney, et al.2002, Collins , et al. 2006). To the author's knowledge, no studies have compared the relative effectiveness of raloxifene versus bisphosphonates or calcitonin in reducing fracture risk. Further comparative effectiveness studies may help to clarify the relative effectiveness of osteoporosis treatments

5.2.4.2 Calcitonin

It has a rapid but short-lived effect on osteoclast function, decreasing the rate of bone resorption. It is given either subcutaneously or intranasally with variations in dose and frequency of administration. Although it reduces the risk of vertebral fractures, this evidence is inconsistent and it is best recommended in those who are unable to tolerate other treatments. Side effects include flushing, vomiting, diarrhea and local irritation, when it is

Injected, administered through nasal crusting or secretion when taken intranasally. Calcitonin is very useful in the acute management of vertebral fractures where it appears to confer analgesic properties, leading to a reduction in pain within two weeks with subsequent improvement in mobility (Sutcliffe, 2005). Calcitonin and parathyroid hormone are involved in the regulation of bone turnover, and hence in the maintenance of calcium balance and homeostasis. By evaluating the efficacy of calcitonin for the treatment and prevention of GIO in a meta-analysis, the results showed that calcitonin prevented bone loss at the spine and forearm by about 3 percent after the first year of therapy.

There was no effect on bone loss at the hip. Calcitonin was not statistically different from placebo at preventing fractures of the spine and long bones, such as hip fractures. Calcitonin was associated with a fourfold greater incidence of side-effects than placebo, mostly nausea and facial flushing. The clinical usefulness of calcitonin for the treatment or prevention of GIO is still unclear. The American Committee of Rheumatology, for example, considers calcitonin as a second-line agent in patients with a low BMD who cannot tolerate bisphosphonates (Vermaat, Kirtschig, 2008)

Calcitonin is a 2-amino-acid peptide that inhibits osteoclast-mediated bone resorption. The salmon form is approximately 40-fold more potent than the human form, due to conformational flexibility Data are available that support the use of salmon calcitonin for treatment of vertebral fractures in women with osteoporosis, though nonvertebral fracture data are generally lacking (Reginster, 2011). Salmon calcitonin nasal spray is FDA-approved for the treatment of osteoporosis at a dose of 200 IU in alternating nostrils each day. It inhibits bone resorption by osteoclasts, thereby preventing bone loss and vertebral fractures, but it has not been shown to reduce nonvertebral or hip fractures. This drug may also decrease the pain associated with acute or sub acute vertebral fractures. There are no contraindications to calcitonin use other than hypersensitivity to the drug; common adverse effects include nasal symptoms and rhinitis in about 12% of patients. Because of the availability of other medications that have better efficacy in fracture reduction, calcitonin is not considered first-line treatment for osteoporosis (Mauck, Clarke, 2006) ‘

In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study, intranasal salmon (100, 200, or 400 IU daily) was compared with placebo in 1255 postmenopausal women with preexisting vertebral compression fractures. After five years of follow-up, 200 IU of salmon calcitonin daily was associated with a 33% decrease in the rate of new vertebral fractures (NNT = 13; RR = 0.67; 95% CI, 0.47–0.97; $p = 0.03$). No significant differences in the rate of new vertebral fractures were demonstrated in patients taking 100 or 400 IU of salmon calcitonin. One factor that may have limited the findings of this study was the high dropout rate. Fifty-nine percent of patients withdrew from the study early, though rates of discontinuation were similar in all treatment groups. In addition to the ability to prevent future vertebral fractures, salmon calcitonin also appears to pos-

sess analgesic activity. Thus, this agent may be useful in the treatment of acute vertebral fractures, in which back pain can be significant (Mac Laughlin, Raehl, 2008)

5.2.2.3 Estrogen / Hormone therapy

Although estrogen replacement therapy (ERT) was used as an antiresorptive therapy for many years for the prevention or treatment of osteoporosis, there was a paucity of data from clinical trials demonstrating a reduction in the risk of fractures, particularly at the hip. Previous recommendations for routine use of estrogen were based on observational studies and Meta analyses that indicated an approximate 30–60% reduction in vertebral and non vertebral fractures with five or more years of ERT use (Mac Laughlin, Raehl 2008).

This therapy comprises Treatment with oestrogen with the addition of cyclical or continuously administered progestogen in women with a uterus. Prospective cohort studies and large randomized clinical trials have demonstrated its efficacy in terms of prevention of post-menopausal bone loss. Findings from the Women's trials performed in the United States (US), have shown beneficial effects of continuous combined oestrogen and progestogen on fracture outcomes This WHI study was curtailed after five years due to the excess number of breast cancer cases; in addition those using HRT were shown to have a higher incidence of coronary events, strokes and pulmonary emboli. On the basis of these findings HRT is no longer recommended as a long-term therapy for the prevention of bone loss or treatment of established disease in the older woman (Sutcliffe, 2005).

The WHI study was the largest randomized, prospective trial to evaluate the risks and benefits of estrogen with and without a progestin in healthy postmenopausal women. The festrogen plus progestin group included 16,608 women with an intact uterus who received either 0.625 mg of conjugated equine estrogen (CEE) plus 2.5 mg of medroxy progesterone acetate or placebo. The estrogen-only group included 10,739 women with a prior hysterectomy, who received 0.625 mg of CEE daily or placebo. After an average follow-up of 5.2 years, estrogen plus progestin was discontinued due to a slightly increased risk of breast cancer (NNH = 237). Based on the results of the WHI study, estrogen should not be used to prevent CHD or as first-line therapy for postmenopausal

osteoporosis and should generally be used at the lowest therapeutic dosage for the shortest time possible to control significant menopausal symptoms (Example hot flashes) Strong consideration of other medications that have been shown to decrease the risk fractures and weighing of the risks and benefits are recommended before using estrogen solely to prevent osteoporosis. (Mac Laughlin, Raehl, 2008).

5.2.2.5 Teriparatide.

Teriparatide is a recombinant form of parathyroid hormone (PTH).It may increase or decrease BMD, depending on the route of administration. Given as an exogenous, intermittent injection, teriparatide increases BMD by stimulating bone formation. The efficacy of teriparatide for reducing the incidence of new vertebral fracture was examined in the FPT Women were eligible for inclusion if they were at least 5 years postmenopausal with at least one moderate or two mild vertebral fractures on radiographs of the thoracic and lumbar spine. For women who had fewer than two moderate vertebral fractures, an additional inclusion criterion was a BMD T-score of the lumbar spine or proximal femur at least -1 SD. Women were randomized to daily injections of teriparatide 20 *ig* (n = 541), teriparatide 40 ng (n = 552) or placebo (n = 544). In the FPT the relative risk of vertebral fracture with teriparatide 20 ng was 0.35 (95% CI 0.22, 0.55). New vertebral fractures occurred in 5% of women in the teriparatide 20 ng group and 14% of women in the placebo group. These results give an RRR of 65 per cent , an ARR of 9 per cent and an NNT of 12, which means that 12 patients would need to be treated for 21 months (the median treatment duration) to prevent one vertebral fracture of any severity. Efficacy against hip fractures has not been demonstrated in a pivotal phase III study with teriparatide, (Neer, et al 2001) The most common adverse effects associated with teriparatide include injection-site pain and swelling (<3.3% of patients), nausea (8.5%), headaches (7.5%), leg cramps (2.6%), and dizziness (8%). These effects resulted in discontinuation rates of 6–19% in clinical trials. Clinical trial data have suggested that the frequency of transient hypercalcemia was 1.5per cent in women and 0 per cent in men given placebo, versus 1 per cent in women and 6 per cent in men treated with teriparatide. Clinical trials of teriparatide have included treatment algorithms to address hypercalcemia that occurs throughout the treatment course, including recommendations for reducing calcium intake to no more than 1000 mg/day or reducing teriparatide injection frequency to once every other day. Clinical manifestations of hyper-

calcemia were not reported among these cases in clinical trials. Allergic reactions, including dyspnea, urticaria, and chest pain, have occurred in less than 1 in 1000 teriparatide recipients. Teriparatide use should be avoided in patients at increased baseline risk for osteosarcoma, such as patients with Paget's disease, unexplained elevations in alkaline phosphatase, , or prior radiation therapy involving the skeleton. Teriparatide should not be used for more than two years because safety and efficacy for longer periods have not been evaluated. Since the commercial launch of teriparatide in December 2002, a worldwide safety monitoring program has identified one confirmed case of osteosarcoma in a patient treated with teriparatide. Causality was not established. This one osteosarcoma case among more than 300,000 patients treated with teriparatide equates to a background annual incidence of 1 in 250,000.40The role of the pharmacist in the management of osteoporosis has been documented primarily in the setting of osteoporosis screening. More recent evidence demonstrates pharmacists taking expanded roles in disease management, such as the development of pharmacist-run clinics. A pharmacist-operated teriparatide clinic has been developed to address the black-box warning, the subcutaneous route, monitoring for potential adverse effects, patient education, and the high cost (example to provide assistance with insurance coverage) The average wholesale price of a month's supply of teriparatide is $629.17, compared with a range of $73.82–$86.81 for antiresorptive agents. Many insurance plans require documentation of failure of or intolerance to previous antiresorptive therapy before they will agree to pay for teriparatide., Lundkvist et al reported that teriparatide monotherapy is cost-effective if used in women who are 69 years or older, have femoral neck T-scores of –3.0 or worse, and have a history of a vertebral fracture. Because of its black-box warning, route of administration, and cost, teriparatide is not considered the drug of choice for typical management of osteoporosis. Appropriate candidates for teriparatide therapy include men and women at high risk of an osteoporotic fracture, patients unable to tolerate antiresorptive therapy, and patients who have worsening BMD or who suffer a fracture while receiving antiresorptive therapy. Consideration may also be given to patients with glucocorticoid- induced osteoporosis, although teriparatide is not labeled for this condition. Teriparatide should be initiated as monotherapy, as most antiresorptive agents given in combination with it have been shown to attenuate its effect. Patient monitoring should include a one-time nadir serum calcium level and annual DXA scans. After two years of teriparatide therapy, bisphosphonate therapy is recommended to

maintain BMD improvements. Prospective studies are needed to assess teriparatide's ability to reduce rates of hip and wrist fractures. Data are also needed to verify teriparatide's long-term safety (Michael, Abu-Baker, 2008)

5.2.2.6 Strontium Ranelate

Strontium ranelate is a divalent strontium salt comprised of two molecules of stable strontium and one molecule of ranelic acid. It is a bone seeking agent capable of increasing bone formation and reducing bone resorption, thereby uncoupling and rebalancing bone turnover in favour of bone formation. In vitro, low-dose (1mmol/L) strontium ranelate for 24 hours stimulated replication of osteoprogenitor cells (by 30–50%) and increased collagen and noncollagen protein synthesis (by 35%) in osteoblasts in cultures from rat calvariae (all $p < 0.05$ vs control). Strontium ranelate also increased ($p < 0.05$ vs control) the differentiation and function of primary murine osteoblasts and promoted ($p < 0.05$ vs control) the differentiation and mineralization of primary human osteoblasts with enhanced osteocyte-like cell formation at some concentrations. The drug triggers mitogenic signals, such as the activation of protein kinase C and p38 mitogenactivated protein kinase and increases the expression of the immediate early genes, c-fos and egr-1, which are involved in osteoblast replication. An in vitro study also suggested that strontium ranelate induced osteoclast apoptosis via the CaSR through a signalling pathway similar to, but also different in certain respects from, that of calcium. This enables strontium ranelate to potentiate calcium-induced apoptosis, and vice versa, acting together with calcium to inhibit bone resorption. In women with osteoporosis in whom long-term treatment with strontium ranelate was shown to improve bone microarchitecture, which may, in turn, improve bone biomechanical competence and explain the antifracture efficacy of strontium ranelate. Significant improvements (all p £ 0.05 vs placebo) in cortical thickness (+18%), trabecular number (+14%), structure model index (-22%) and trabecular separation (-16%), as assessed by microcomputer tomography, were observed in 3-year biopsies from 41 women who received strontium ranelate 2 g/day or placebo in clinical trials. Treatment with strontium ranelate 2g/day for 2 months had no significant effect on in vitro bleeding time or most other haemostatic parameters or anticoagulant proteins in 35 elderly women (aged ‡65 years) with osteoporosis. In a small prospective cohort study, strontium ranelate 2 g/day for 12 months was shown to increase ($p = 0.033$) lumbar spine BMD (and reduce bone markers to baseline

levels. In 19 (evaluable) women with postmenopausal osteoporosis who had previously been treated with teriparatide 20 mg/day for 18 months and had experienced a significant ($p < 0.001$) increase in BMD during this period, suggesting that strontium ranelate potentially could be used for sequential treatment of patients. Previous treatment with bisphosphonates may blunt the effect of strontium ranelate on BMD for up to 6 months at the spine and for at least 12 months at other sites, according to a study in women with osteoporosis. After 6 and 12months of treatment with strontium ranelate, bisphosphonate- naive women ($n = 56$) had significant ($p £ 0.002$) increases in BMD at the spine (2.4% and 5.6%), total hip (1.9% and 3.4%) and heel (2.9% and 4.0%), whereas women previously treated with bisphosphonates ($n = 52$) had a significant ($p = 0.002$) increase in BMD only at the spine (2.1%) at the 12-month time point. The effect of strontium ranelate therapy on BMD at each of these sites was significantly ($p < 0.05$) more favourable in bisphosphonate-naive women than in those previously treated with bisphosphonates, at both the 6- and 12-month time point.. Strontium ranelate also produced improvements in the bone formation, microstructure and BMD of the fracture callus, compared with no treatment. In women with osteoporosis, long-term (3 years) treatment with strontium ranelate 2 g/day did not adversely affect primary bone mineralization. Mineral apposition rate increased by 9% ($p = 0.019$) in cancellous bone and by 10% in cortical bone with strontium ranelate relative to placebo, as assessed by 2-dimensional histomorphometric analyses of bone biopsies. In another randomized, double-blind trial in 125 Asian women with osteoporosis, serum levels of bone ALP increased from baseline with strontium ranelate 2 g/day and decreased slightly from baseline with placebo after 6 and 12 months of therapy, with significant ($p £ 0.003$) between-group differences being observed at both time points (15% and 26% at 6 and 12 months. There was no significant between-group difference in the change from baseline in levels of CTX, which increased slightly from baseline with both strontium ranelate and placebo at 6 and 12 months. The short-term effect of strontium ranelate on some biochemical markers of bone remodeling appears to be associated with long-term changes in BMD, but not fracture incidence, in women with postmenopausal osteoporosis, according to data from a post hoc pooled analysis ($n = 2373$) of two large clinical trial. it has been suggested that monitoring the clinical efficacy of strontium ranelate therapy with the use of markers of bone turnover in the individual patient may not be appropriate. The potential for strontium ranelate to be used in the treatment of postmenopausal osteoporosis was

established in a 2-year, randomized, double blind, placebo-controlled, multicentre, dose ranging (0.5–2mg/day) study (n = 353). On the basis of the findings of this phase II trial, a strontium ranelate dosage of 2 g/day was selected for further clinical evaluation The absorption of strontium is dose-dependent, but the increases in peak plasma concentration (Cmax) and the area under the concentration time curve (AUC) are less than dose-proportional over a dose range of 0.25–8 g, probably because of the saturation of an active absorption process. Following a single dose of strontium ranelate 2 g, the Cmax (»6mg/L) of strontium was reached in 3 hours, with steady state being achieved after 2 weeks of treatment. After an oral dose of strontium ranelate 2 g, the absolute bioavailability of strontium is »25% (range 19 27%). In postmenopausal women, strontium has an accumulation ratio of »9 when the AUC from time 0 to 10 hours after the first dose was compared with that at steady state. Intake of calcium or food with strontium ranelate administration reduces the bioavailability of strontium by »60–70% compared with dose administration 3 hours after a meal. Owing to the relatively slow absorption of strontium, food and calcium intake should be avoided for a period of time both before and after strontium ranelate administration. (Deeks, Dhillon, 2011)

5.2.2.7 Calcitriol

Calcitriol (1, 25-(OH) 2D3) is a hormone produced from VitD3 (Cholecalciferol). Stimulates intestinal absorption of calcium and phosphate and mobilizes calcium and phosphate from hydroxyapatiteby stimulating bone resorption. These features enable restoration of blood levels of calcium and phosphate to normal when the two ions are low. It has been reported that 1, 25-(OH) 2D3 induces fusion and differentiation of macrophages. An effect that has been interpreted to be the natural role of 1, 25-(OH)2D3 to induce osteoclastogenesis from the colony-forming unit for the granulocyte macrophage series in the bone marrow. It has been reported that although the osteoclast is the main bone-resorbing cell, it does not contain receptors for the main bone resorbing hormones, calcitriol and parathormon. In bone tissue, the anabolic effect of calcitriol is to increase the rate of mature osteoid production, and in the presence of normal blood calcium (Ca) and phosphate (PO4), this osteoid becomes mineralized. Histomorphometric studies of osteoporotic patients treated with calcitriol showed a similar increase in both osteoclasts and osteoblasts per surface. In a retrospective analysis of 26 osteoporotic women, Shi-

raki and colleagues found that radial bone density increased in about half of the treated patients receiving 0.5 to 1.0 mg 1a-OH-D3 daily. Few randomized placebo-controlled trials of treatment of osteoporosis by calcitriol have addressed the clinically important issue of prevention of fractures. Tilyard and colleagues carried out a study in 622 women (50–79 years) over 3 years. The patients received either 0.25 mg calcitriol twice a day (314 patients) or 500 mg elemental calcium gluconate twice a day. Nearly 95% of the women treated with calcitriol were free of new fractures, compared with 80% of the calcium-treated group at the end of 3 years. Decline of fracture rate in patients under treatment with calcitriol was also found by other investigators. Thirty-seven patients (26 females, 11 males, mean age66.4 years) with chronic obstructivepul monary disease under treatment with corticosteroids for more than 2 years with 5–10 mg aprednisolone daily and osteopenia or osteoporosis confirmed by bone densitometry (lumbar spine or femoral. (Mirzaei, Zajicek, Knoll, et al 2003)

5.2.3 New treatments approved by FDA

5.2.3.1 Denosumab

It is the most recent antiresorptive agent to be approved for the treatment of osteoporosis. Denosumab is a monoclonal antibody against RANK-L. RANK-L stimulates the differentiation, activity and survival of osteoclasts, and is implicated in the pathogenesis of postmenopausal osteoporosis and other skeletal disorders associated with a high rate of bone remodeling. It has a potent action in slowing the rate of bone remodeling. The FREEDOM trial recruited 7868 postmenopausal women aged 60-90 years with a lumbar spine BMD T-score of less than -2.5 to -4.0 SD. Approximately 23% of the FREEDOM population had at least one prevalent vertebral fracture at the time of entry into the study. Women were randomized to receive either denosumab 60 mg subcutaneously (n = 3902) or placebo (n = 3906) every 6 months. The primary end point was new vertebral fractures at 3 years. The relative risk of vertebral fracture with denosumab was 0.32 (95% CI 0.26, 0.41). New vertebral fractures occurred in 2% of women in the denosumab group and in 7% of women in the placebo group. After 3 years, the postmenopausal osteoporotic women receiving denosumab had a slightly reduced risk of hip fracture with a cumulative incidence of 0.7 per cent in the denosumab group versus 1% in the placebo group. (Reginster, 2011)

5.2.3.2 Lasofoxifene

Evidence for lasofoxifene in the treatment of postmenopausal osteoporosis comes from the PEARL study. PEARL recruited 8556 women between the ages of 59 and 80 years with a BMD T-score of-2.5 SD or less at the lumbar spine; a prevalent vertebral fracture was not an entry requirement and only 28 per cent had at least one prevalent baseline radio graphically defined vertebral fracture. Women were randomized to lasofoxifene at a dose of either 0.25 or 0.5 mg/day or placebo. Only the results for the 0.5 mg/day dose were presented here because these were the marketed dose in Europe. The trial was planned to continue for 5 years; vertebral fracture was the primary endpoint for the first 3 years of the trial. The hazard ratio for vertebral fracture with lasofoxifene 0.5 mg/day was 0.58 (95% CI 0.47, 0.70), indicating an RRR of 42 per cent. Lasofoxifene 0.5 mg/day was associated with a reduction in the absolute incidence of radiography vertebral fractures at 3 years of 9.5 (13.5 vs 23 fractures per 1000 patient-years; 95% CI 5.2, 13.7). The PEARL trial data allow calculation of relative and absolute risk over 5 years (but not 3 years). Therefore, the RRR for vertebral fracture over 5 years with lasofoxifene is 40 per cent, with an ARR of 4 per cent and an NNT of 26. In the same study, lasofoxifene failed to demonstrate a significant effect against hip fractures (hazard ratio 0.77 95% CI 0.46, 1.27; not significant). (Reginster, 2011)

6. METHODOLOGY

This chapter deals with the methods of design study. This chapter deals with the methods and design of the study. The study is a qualitative study in which the methods used in the entire study are literature review and content analysis.

Methodology is generally the guideline for solving problems with specific components such as phases, tasks, methods, techniques and tools. It is also the analysis of the principle of methods, rules and postulates employed by a discipline.(Wikipedia)

6.1 Qualitative analyses

A method of inquiry employed in many different academic disciplines, traditionally in the social sciences but also in market research and further contexts. It produces information on the particular cases studied and any more general conclusions are only propositions (informed assertions). It can be used to seek empirical support for such research hypotheses. (Wikipedia). Qualitative study broadly defined means any kind of research that produces findings not arrived at by means of statistical procedures or other means of quantification Sutcliffe. (Golafshani, 2003)

In this study, qualitative research method was used in data collection where by the methods used allowed the evaluator of this study to concentrate on the selected issues, cases or events in depth and in details.

6.2 Content analysis

It is a methodology in the social sciences for studying the content of communication. It is summarizing, quantitative analysis of messages that relies on the scientific method and is not limited as to the types of variables that may be measured or the context in which the message are created or presented.(Wikipedia). Content analysis usually refers to analyzing text (interview, scripts, diaries, articles, journals, or documents) rather than observation-based field notes. More generally content analysis is used to refer to any qualitative data reduction and sense making effort that takes a volume of qualitative material and attempts to identify core consistencies and meanings (Patton, 1990).

The method used for this study was content analysis therefore author grouped the common themes that emerged from the findings into different categories which are as follow: sub category, category and main category. The main idea was to analyze the findings which intended to answer the research questions.

The articles that were collected from this study were selected carefully by the author and the previous researched articles considered in the study were those which were clinical trials based on postmenopausal women and elderly men aged 65 and older. The credibility of previous articles used in this study was put into consideration which is the author, year of publication and the presentation of the findings.

A systematic search was conducted through electronic databases EBSCO Host, Cinahl Ebsco and Google scholar for papers which were published from the year 2001-2011.The search was conducted to review articles which had information on the pharmacological treatment and non pharmacological treatment of osteoporosis in the elderly mostly the ones who are at the postmenopausal stage. The subject terms or keywords used were; Osteoporosis* postmenopausal* treatment* medicine research* or drugs* old age*or aging*.

The data that was collected for the study was studied carefully by the author. The whole process was divided into 3 processes for the 3 categories. The main idea behind this was to group the data into sub groups and link the sub groups to main part which are the research questions for the study.

6.3 Study Outcome

The study engulfs around the subject of osteoporosis in the elderly (65+), its prevention and the treatments already approved and available in the market. The aims and objectives are achieved by the use of deductions from the previous research studies under literature review through analyzing the findings

6.4 Problems encountered

The author encountered difficulties in obtaining articles and books that discussed content analyses and full text medical articles with clinical trials and books that discussed the current pharmacological treatments of osteoporosis. Most of the articles that were found were already reviewed by several other authors therefore the findings were not diverse. Another problem was that most of the current articles were not accessible freely so it was difficult to get the most current articles with the most current information.

However with the few articles that the author was able to access, the author was able to answer the two research questions posed for this study.

6.5 Ethical Consideration

Prior to writing the study the authors studied thoroughly and understood the Helsinki Declaration. The scientific published articles that were used as the basis for this study were reported in truth throughout the study. The author has fully and clearly documented all the sources for idea and words and texts that have been used in this study. References gotten directly from the articles and books used for this study have been quoted and written in inclusive of the authors name and the year of publishing. The author has fully documented sources for ideas and words used in the study

6.6 Validity and Reliability

Validity has been defined as truthfulness. Does the test measure what it purports to measure? It also refers to the extent to which certain inferences can be made from test scores or other measurement. (Mehrens, Lehman, 1987). It has also been defines as the degree to which they accomplish the purpose for which they are being used. (Worthen et al., 1993)

Reliability has been defined as the degree of consistency between two measures of the same thing. (Mehrens, Lehman, 1987).

The measure of how stable, dependable, trustworthy, and consistent a test is in measuring the same thing each time (Worthen et al., 1993)

Joppe (2000) defines reliability as: The extent to which results are consistent over time and an accurate representation of the total population under study is referred to as reliability and if the results of a study can be reproduced under a similar methodology, then the research instrument is considered to be reliable.

The validity of a content analysis study refers to the correspondence of the categories to the conclusions, and generability of results to the theory. The validity of categories in

simplicity concept analysis in particular, is searched by utilizing multiple classifiers to arrive at an agreed upon definition of the category. In the study the author carefully studied the published articles that were chosen for this study. The results that were relevant and corresponding to the research questions were grouped into different categories as explained in the methodology part of this work.

The published articles were retrieved from reliable databases that contain scientific research work done by professionals in the medical field. The results found in the study have all emerged from scientific articles that were used for this study and the author has not included any other sources in the results. The author has neither used past experiences nor the authors' knowledge to influence or alter the results.

6. 7 Sample Process

At the beginning of the search a trial was made to find data about elderly and osteoporosis. The author used database EBSCO host to find the articles which were relative to the study. The subject terms were osteoporosis* risk factors* prevention* treatment*
This search yielded 57905 hits. The author then conducted another search through EBSCO host database this time limiting the search to full text articles and this yielded 2787 hits. The author was interested in the articles which were no older than ten years, so the search was restricted to the year 2001 to 2011, this yielded 1095 hits, the author also restricted the search to subject terms postmenopausal* elderly* (65 and older).The search yielded 37 hits. These articles were reviewed again this time taking into consideration that the author was only interested in the articles that discussed current osteoporosis risk factors and medication for osteoporosis prevention and treatment. The author came up with 7 hits which were found to be relevant to the study and produced clear information to the growth of the study.
The author used CINAHL EBSCO search engine with the subject terms osteoporosis*risk factors* prevention* treatment*elderly* the search produced 422 hits. The author further limited the search to the year 2001 to 2011. This search yielded 378 references. The author was interested in the full text articles and the search yielded 27 hits. The 7 best articles were chosen. Another search using Google Scholar Advanced was conducted with the subject terms osteoporosis* risk factors* prevention* treatment* this yielded 487,000 hits. The author limited the search to timeline of 2001 to 2011 and also

to full text and this yielded yielded19 142 hits. The author was interested in the articles based on the menopausal elderly women and elderly men of age 65 and above and from those 4 best articles were chosen.

The author ended up with 19 articles which were yielded by the search. The articles have been described in the table below

Table 3. Summary of the articles used in the analyses

Authors	**Articles**	**Contents and Results**
DontasI.A, yiannakopolouous C.K(2007)	Risk factor and prevention of osteoporosis related fractures	The article is about Prevention of osteoporosis and how it should ideally begin in childhood, aiming to achieve high peak bone mass accompanied by an inherently healthy lifestyle throughout life, in order to minimize bone loss during middle and third age, and in parallel to avoid or diminish other fracture risk factors
Tauseef Chaudhri(2006)	Identifying nutritional and lifestyle risk factors associated with the development of osteoporosis in women of Asian origin	The objective of this study was to identify the risk factors associated with the occurence of osteoporosis in Kenyan A sian women seen in Agah Khan University Hospital, Nairobi Kenya and the findings were that the risk factors were identified were age, waist size, hip size, BMI, low physical activity, and use of prescription drugs.
Spangler , et al(2011)	Calcium supplementaion in postmenopausal women to reduce the risk of osteoporotic fractures	The purpose of this article was to evaluate the effects of calcium supplementation for prevention of osteoporosis-related fractures in postmenopausal women and the results indicated that calcium supplementation does not significantly reduce fracture risk in postmenopausal women. And evidence from the same studies suggests that beneficial effects on fracture risk may be seen in women who are adherent to therapy and Postmenopausal women should continue calcium supplementation

		to reduce osteoporosis risk.
Mac Laughlin, Eric. J, RaehlCynthia L(2008)	ASHP Therapeutics position statement on the prevention and treatment of osteoporosis in Adults	The article is a review on prevention and treatment of osteoporosis in Adults. The author encourages that health care professional to educate patients about risk factors associated with osteoporosis. They further encourages health care professionals to identify and triage at risk patients for osteoporosis screening and diagnosis .
JunIwamoto, Yoshihiro,et al (2008)	Hip fracture protection by alendronate treatment in postmenopausal women with osteoporosis	The purpose of this paper was to discuss the efficacy of alendronate against hip fractures and the mechanism for this antifracture efficacy in postmenopausal women with osteoporosis results states that alendronate strongly suppresses bone turnover and subsequently increases hip BMD, decreases cortical porosity, improves parameters of hip structure, and produces more uniform in cortical bone. A once-weekly regimen of alendronate administration provides better patient compliance and persistence with the treatment than the once-daily dosing regimen, leading to greater efficacy against hip fractures. Thus, the efficacy of alendronate against hip fractures has been confirmed in postmenopausal women with osteoporosis, especially with a once-weekly dosing regimen.
S.Boonen, Vanderschueren et al (2006)	Osteoporosis management a prospective based on biosphosphonates data methods	This article describes the evidence base that supports. The types of individuals who should receive calcium and vitamin D supplements are those patients with documented osteoporosis receiving antiresorptive or anabolic treatment, patients receiving glucocorticoids and individuals with or at high risk of calcium and/or vitamin D insufficiencies, in particular older women and men. The results on evidence have shown that. Calcium and vitamin D supplementation is most effective when targeted to those who are receiving antiresorptive or anabolic osteoporosis Therapy, are being treated with glucocorticoids and are likely to be calcium or vitamin D insufficient.

RahmaniPoupak, Morin Suzanne (2009)	Prevention of osteoporosis related fractures among postmenopausal women and older men	This article addresses the approach to managing osteoporosis in postmenopausal women and older men. The findings were that Pharmacologic agents for the treatment of osteoporosis are effective in preventing fractures in postmenopausal women and elderly men at high risk (10-year absolute risk of any osteoporosis-related fracture > 20%).
Deutschmann H.et al (2002)	Impact of identified possible risk factors on bone mineral density	The article was to determine whether the use of more elaborate diagnostic tests can identify possible risk factors for secondary osteoporosis and to evaluate the impact of these possible risk factors on the severity of bone disease in the study population. Findings were that one or more possible risk factors for osteoporosis were revealed. The most common were lactose malabsorption, disturbed exocrine pancreatic function and renal tubular disturbances, including renal hypercalciuria, incomplete renal tubular acidosis and mild phosphate diabetes
Bito C. M Moran, Bastistella L. R(2005)	Effects of alendronate on bone mineral density in spinal cord injury patients	The aim of the article was to evaluate the effect of alendronate on bone mineral density in chronic spinal cord injury (SCI) patients. Findings were that the use of alendronate had a positive effect on bone mineral density in SCI patients and therefore represents a potential tool for prevention and treatment of osteoporosis in this population.
Deane Andrew et al (2007)	The impact of Vitamin D status on changes in bone mineral density during treatment with bisphosphonates and after discontinuation following long term use in postmenopausal osteoporosis	The aim was to assess the impact of vitamin D status on changes in bone mineral density (BMD) in firstly patients with post-menopausal osteoporosis on bisphosphonates and secondly following discontinuation of bisphosphonates after long-term use. Findings were that optimal serum 25 (OH) vitamin D concentration may lead to further reduction in bone loss at the hip in patients on bisphosphonates
Recker R, et al (2005)	Treatment of early postmenopausal womenwith bisphosphonates	The articles talks about bisphosphonates as being the most commonly prescribed therapy for the prevention and treatment of osteoporosis and affect bone formation,

		primarily through a reduction of activation frequency and increases in secondary mineralisation.
Cadarette Suzanne et al (2008)	Relativeeffectiveness of osteoporosis drugs for preventing non vertebral fractures	The aim of the article was to compare the relative effectiveness of osteoporosis treatments to reduce nonvertebral fracture risk among older adults. Findings were that differences in fracture risk between risedronate or raloxifene and alendronate were small. Nasal calcitonin recipients may have a higher risk for nonvertebral fractures compared with alendronate recipients
Black M.D, Delmas P. D, et al (2007)	Once-yearly zolendronic acid for treatment of postmenopausal osteoporosis	The aim was to assess the effects of annual infusions of zoledronic acid on fracture risk during a 3-year period. Treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% during a 3-year period
Lyes K.W,et al (2007)	Zolendronic acid in reducing clinical fractur and mortality after hip fracture	The aim was to determine the effects of zoledronic acid on clinical fractures and mortality after hip fracture. Findings were that an annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and with improved survival
Chesnut Charles H (2006)	The role of salmon calcitonin in the treatment of vertebral fractures	The article was to determine the role of salmon calcitonin in the treatment of vertebral fractures. Findings indicated that the mechanism of action for salmon calcitonin nasal spray appears to be less related to an increase in BMD, but rather to its inhibition of bone resorption and to the preservation of bone micro architecture.
VermaatHester, KirtschigGudula (2008)	Prevention and treatment of glucocorticoid induced osteoporosis in daily dermatologic practice	The aim of the article was to provide an update of the recent advances in the prevention of GIO in dermatologic practice. Findings were that prophylaxis of osteoporosis needs to be started early during treatment with GCs. Calcium and vitamin D supplements in all patients on systemic GCs and bisphosphonates in patients who take GCs for more than 3 months are practical and effective measures

Mauck Karen. F, Clarke Bartl I (2006)	Diagnosis, screening, prevention and treatment of osteoporosis	The purpose of the article was to provide overview of the diagnosis, screening, prevention, and treatment of osteoporosis. It states that clinicians need to be vigilant in instituting primary prevention measures for those at high risk for osteoporosis and in instituting treatment for patients diagnosed as having the disease either by screening or a history of fracture
Michael Kane, Abu Baker (2008)	Teriparatide in the treatment of osteoporosis	The purpose was to review the efficacy, safety, and cost of teriparatide in the treatment of osteoporosis. Findings were that teriparatide offers a therapeutic option for patients at high risk of an osteoporotic fracture and for patients who are intolerant of or unresponsive to antiresorptive therapy.
Deeks Emma, Dhillion Sohita (2010)	The effects of PTH or strontium ranelate on bone formation markers in postmenopausal women with primary osteoporosis	Aim was to explore the effects of PTH compared with strontium ranelate on bone remodelling as measured by bone remodelling markers in postmenopausal women with osteoporosis. Findings: PTH had a more rapid and higher effect on bone formation markers compared to SR, indicating that SR has a different mode of action on bone remodelling than the bone building agent PTH in postmenopausal women with osteoporosis

7. PRESENTATION OF RESULTS

This chapter consists of the results that were found in this study. The results have been divided into 3 parts according to the three research questions.

Question 1. What are the current risk factors for osteoporosis in the elderly and how they can be controlled?

Most modifiable risk factors directly impact bone biology and result in a decrease in bone mineral density (BMD), but some of them also increase the risk of fracture independently of their effect on bone.. Although fixed risk factors cannot be changed, people need to be aware of them so that they can take steps to reduce bone mineral loss

SUB-CATEGORY	CATEGORY	MAIN-CATEGORY
Inadequate exercise, inadequate nutrition, Calcium and vitamin D deficiency, smoking, alcohol abuse, certain drugs and medications and life styles, low body weight	Can be controlled	Current risk factors for osteoporosis in the elderly

SUB-CATEGORY	CATEGORY	MAIN-CATEGOEY
Age, gender, race, early menopause, family history.	Cannot be controlled	Current risk factors for osteoporosis in the elderly

Question 2. What are the classifications of osteoporosis medications and their effects on the disease?

From this study, it has clearly shown that osteoporosis medications are classified and categorized in different classes and have different purposes. This categorization have clearly helped to answer the second question of this study

SUB-CATEGORY	CATEGORY	MAIN-CATEGORY
Alendronate	Bisphosphonate	Treatment and Prevention
Risedronate		
Ibandronate		
Raloxefine	Selective estrogen receptor modulator	
Denosumb	Miscellaneous bone resorption inhibitor	
Strontium ranelate	Dual acting bone agent	
Calcitriol	Parathyroid hormone and analogs	

SUB-CATEGORY	CATEGORY	MAIN-CATEGORY
Teriparatide	Parathyroid hormone and analogs	Treatment

Calcitonin Zolendronate	Calcitonin Bisphosphonate	

SUB-CATEGORY CATEGORY MAIN-CATEGORY

Estrogen Calcium & Vitamin D	Hormone Replacement Therapy Vitamin and mineral combination	Prevention

Question 3. What are the current approved medications for osteoporosis and their methods of administration?

This study has also found that Food and Drug Administration (FDA) have already approved several medications to the treatment of osteoporosis and their methods of administration in the elderly. These approved medications are classified into categories in which answers the third research question of this study.

MAIN CATEGORY SUB-CATEGORY CATEGORY

Bisphosphonate	Alendronate	P: 5 mg Daily, 35 mg Weekly tablet T: 10 mg Daily, 70 mg weekly tablet
	Risendronate	P,T: 5 mg Daily, 5 mg, 35 mg weekly tablet
	Ibandronate	P,T 2.5 mg Daily, 150 mg Monthly tablet/3 IV
Dual acting bone agent	Strontium ranelate	P,T:2 g Daily soluble sachet(2 Months)
Monoclonal antibody	Denosumab	P,T: 60 mg Six months subcutaneous IV
Selective oestrogen receptor	Raloxifene	P,T: 60 mg Daily tablet
Parathyroid hormone & analogs	Calcitriol	P.T: 0 .5 to 1.0 mg Daily (1a-OH-D3)

MAIN CATEGORY SUB-CATEGORY CATEGORY

Vitamin& Mineral Hormone replacement therapy	Calcium & Vitamin D Estrogen	P: 1200mg Ca & 1200 IU Vi Daily tablets P: 0.625 (CEE) Daily Formula

MAIN CATEGORY	SUB-CATEGORY	CATEGORY
Bisphosphonate	Zolendronate	T: 5 mg Annual IV infusion
Calcitonin	Calcitonin	T: 200µ Daily nostril spray
Parathyroid hormone & analogs	Teriparatide	T: 20/ig Daily injection

.

Greater choices of therapies with potentially fewer side effects are now available. Fracture risk can be reduced by 40 to 60 per cent by identification of osteoporosis and use of osteoporosis medications in the elderly. Individual drugs may have contraindications and potential side effects and will not suit all patients.

Alendronate, risedronate, denosumab, strontium ranelate and zoledronate have an evidence base for the reduction of fractures. Alendronate, teriparatide and zoledronate are approved for the prevention and treatment of corticosteroid-induced osteoporosis in men and women. Risedronate is approved for the prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women. Other approved pharmacological interventions for postmenopausal women include calcitonin, calcitriol and hormone replacement therapy (HRT).

Generic bisphosphonate is usually the first choice of therapy, partially because of its low cost and long-term base of clinical trial data. Patients with abnormalities of the esophagus are not suitable for bisphosphonate treatment and those who develop swallowing problems or pain behind the sternum are advised to stop treatment and consult their prescriber. Other therapies, such as risedronate, denosumab or strontium ranelate may be required in women (Elliott, 2011)

.

International guidelines agree that agents that have been shown to decrease vertebral, nonvertebral and hip fractures should be used preferentially over agents that only demonstrate vertebral antifracture efficacy. This is the case for alendronate, risedronate, zoledronic acid, and denosumab and strontium ranelate

7.1 Alendronate

Alendronate 70mg administered once weekly and 35mg twice weekly are as effective at increasing BMD as 10 mg/day in the patient group. Absorption and disposition of alendronate over the dosage range 5 to 80mg are linear. Beverages (other than water), food and calcium supplements all reduce absorption of alendronate. The drug is either excreted by the kidneys, the only route of elimination, or taken up and sequestered by bone, from where it is slowly released. The mean steady-state volume of distribution of alendronate, excluding bone, is estimated to be at least 28L. (Sharpe, Noble, et al 2001). Alendronate is also a suitable treatment option for primary osteoporosis in men and for corticosteroid-induced osteoporosis in both men and women. (Miriam Sharpe, Stuart Noble et al 2001). The use of alendronate had a positive effect on bone mineral density in SCI patients and therefore represents a potential tool for prevention and treatment of osteoporosis in this population. (Brito, Battistella, 2005).

7.2 Risedronate

Retrospective analyses showed that risedronate significantly reduced the incidence of nonvertebral and clinical vertebral fractures within 6 months. Treatment with risedronate for 36 months reduced the risk of vertebral fractures by 41 per cent and non vertebral fractures by 39 per cent relative to placebo in women with at least one existing vertebral fracture17 and the risk of hip fractures by 40 per cent relative to placebo in women aged 70 to 79 with osteoporosis. (Boonen, et al, 2010). Results from observational studies suggest that risedronate may reduce the risk for nonvertebral fracture (clavicle, hip, humerus, leg, pelvis, and wrist) within 12 months more effectively than alendronate or nasal calcitonin (Cadarette, et al 2008)

7.3 Zoledronic acid

The incidence of any clinical fracture, clinical vertebral, or nonvertebral fracture in postmenopausal women aged 75 and older was significantly lower in the ZOL group

than in the placebo group over 3 years (P<.001, P<.001, and P=.002, respectively) in HORIZON trial. A similar finding has been shown for any clinical fracture and clinical vertebral fractures at 1 year (P=.03 and P=.009, respectively), but the incidence of non-vertebral fracture at 1 year and hip fracture at 1 and 3 years was lower for the ZOL group although not significantly (Black, et al, 2007). In another trial that involved men and women with a recent hip fracture. Zoledronic acid was also found to decrease mortality by 28 percent compared with placebo in the study involving patients with a recent hip fracture (number needed to treat = 29). (Lyles, et al, 2007)

7.4 Ibandronate

Intermittent ibandronate extends the range of pharmacological therapies for the treatment and prevention of postmenopausal osteoporosis. It inhibits osteoclast-mediated bone resorption. In clinical trials in postmenopausal women with osteoporosis, approved oral and intravenous ibandronate dosage regimens reduced bone turnover, and increased lumbar spine and proximal femur bone mineral density (BMD) and mechanical strength. (Frampton, Perry, 2008). Preclinical studies initially revealed the feasibility of extending the between-dose interval. Subsequent clinical studies have provided further evidence of the positive effects of extended-interval ibandronate administration in reducing the risk of vertebral fractures through increasing bone mineral density and reducing bone turnover without compromising bone quality. (Chestnut, 2006). The once daily oral formulation of ibandronate is not commercially available. Patients prescribed once monthly oral ibandronate should take their tablet preferably on the same date each month and after an overnight fast (6 hours or more) and /or 1 hour or more before the first food and drink of the day or any other oral medication or supplement. The tablet should be taken with plain water while sitting or standing in an upright position and patients should not lie down for 1 hour afterwards. (Frampton, Perry, 2008).

7.5 Raloxifene

Raloxifene was the first SERM approved for the prevention and treatment of osteoporosis in postmenopausal women. In the MORE study, the relative risk of vertebral fracture with raloxifene was 0.70 (95% CI 0.6, 0.9). New vertebral fractures occurred in 113 (15%) women in the raloxifene group and in 163 (21%) women in the placebo group. In a meta-analysis of 7 trials in which postmenopausal women were given raloxifene or placebo, raloxifene was associated with a risk reduction in vertebral fractures (RR 0.60, 95% CI 0.50–0.70; number needed to treat = 2381 to 99 across the range of fracture risk for 2 years of treatment).There was little effect of raloxifene on the risk of other fractures. (Cranney. et al.2002, Connor, et al, 2006).

7.6 Calcitonin

Calcitonin is very useful in the acute management of vertebral fractures where it appears to confer analgesic properties, leading to a reduction in pain within two weeks with subsequent improvement in mobility (Sutcliffe 2005). By evaluating the efficacy of calcitonin for the treatment and prevention of GIO in a meta-analysis, the results showed that calcitonin prevented bone loss at the spine and forearm by about 3 percent after the first year of therapy. The American Committee of Rheumatology, for example, considers calcitonin as a second-line agent in patients with a low BMD who cannot tolerate bisphosphonates (Vermaat, Kirtschig, 2008).In the ability to prevent future vertebral fractures, salmon calcitonin also appears to possess analgesic activity so this agent may be useful in the treatment of acute vertebral fractures, in which back pain can be significant (Mac Laughlin, Raehl 2008)

7.7 Estrogen / Hormone therapy

Findings from the Women's trials performed in the United States (US) have shown beneficial effects of continuous combined oestrogen and progestogen on fracture outcomes. On the basis of these findings HRT is no longer recommended as a long-term

therapy for the prevention of bone loss or treatment of established disease in the older woman (Anne Sutcliffe 2005). Strong consideration of other medications that have been shown to decrease the risk fractures and weighing of the risks and benefits are recommended before using estrogen solely to prevent osteoporosis. (Mac Laughlin, Raehl 2008)'

7.8 Teriparatide.

Teriparatide use should be avoided in patients at increased baseline risk for osteosarcoma, such as patients with Paget's disease. Teriparatide should not be used for more than two years because safety and efficacy for longer periods have not been evaluated. Since the commercial launch of teriparatide in December 2002, a worldwide safety monitoring program has identified one confirmed case of osteosarcoma in a patient treated with teriparatide. Lundkvist et al reported that teriparatide monotherapy is cost-effective if used in women who are 69 years or older, have femoral neck T-scores of –3.0 or worse, and have a history of a vertebral fracture. Appropriate candidates for teriparatide therapy include men and women at high risk of an osteoporotic fracture, patients unable to tolerate antiresorptive therapy, and patients who have worsening BMD or who suffer a fracture while receiving antiresorptive therapy. . Prospective studies are needed to assess teriparatide's ability to reduce rates of hip and wrist fractures. Data are also needed to verify teriparatide's long-term safety (Stroup, et al, 2008)

7.9 Strontium Ranelate

This is used in women with osteoporosis, in whom long-term treatment with strontium ranelate was shown to improve bone microarchitecture, which may, in turn, improve bone biomechanical competence and explain the antifracture efficacy of strontium ranelate. In a small prospective cohort study, strontium ranelate 2 g/day for 12 months was shown to increase ($p = 0.033$) lumbar spine BMD (and reduce bone markers to baseline levels. In 19 (evaluable) women with postmenopausal osteoporosis who had previously been treated with teriparatide 20 mg/day for 18 months and had experienced a signifi-

cant ($p < 0.001$) increase in BMD during this period, suggesting that strontium ranelate potentially could be used for sequential treatment of patients. The potential for strontium ranelate to be used in the treatment of postmenopausal osteoporosis was established in a 2-year, randomized, double blind, placebo-controlled, multicentre, dose ranging (0.5–2mg/day) study (n = 353). (Deeks, Dhillon, 2011)

7.10 Calcitriol

Histomorphometric studies of osteoporotic patients treated with calcitriol showed a similar increase in both osteoclasts and osteoblasts per surface. Few randomized placebo-controlled trials of treatment of osteoporosis by calcitriol have addressed the clinically important issue of prevention of fractures. Patients received either 0.25 mg calcitriol twice a day, (314 patients) or 500 mg elemental calcium gluconate twice a day. Nearly 95 per cent of the women treated with calcitriol were free of new fractures, compared with 80 per cent of the calcium-treated group at the end of 3 years. Decline of fracture rate in patients under treatment with calcitriol was also found by other investigators. (Mirzaei, et al, 2003)

7.11 Denosumab, Lasofoxifene

These are most recent approved drugs by the FDA. Denosumab has a potent action in slowing the rate of bone remodeling. In the FREEDOM trial. After 3 years, the postmenopausal osteoporotic women receiving denosumab had a slightly reduced risk of hip fracture with a cumulative incidence of 0.7 per cent in the denosumab group versus 1 per cent in the placebo group, giving an ARR of 0.3 per cent and an NNT of 334.(Reginster 2011)

Lasofoxifene 0.5 mg/day was associated with a reduction in the absolute incidence of radiography vertebral fractures at 3 years of 9.5 (13.5 vs. 23 fractures per 1000 patient-years; 95% CI 5.2, 13.7). I n the PEARL study, lasofoxifene failed to demonstrate a significant effect against hip fractures (hazard ratio 0.77 95% CI 0.46, 1.27; not significant). (Reginster 2011)

8. DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Osteoporosis is a largely treatable condition and with a combination of lifestyle changes and appropriate medical treatment, many fractures can be avoided. Osteoporotic fractures are a cost in terms of morbidity and mortality for older people and financially for the health economy. Identification of high-risk patients and the provision of interventions are important steps in the prevention of fractures and resultant frailty. New and emerging medicines and approaches offer a wider choice of treatment options.

Pharmacologic agents for the treatment of osteoporosis are effective in preventing fractures in postmenopausal women and elderly men at high risk (10-year absolute risk of any osteoporosis-related fracture > 20%). All of the proposed interventions are cost-effective compared with no treatment in postmenopausal women. The gains associated with each intervention are strongly related to the age of the patient, the presence of fracture and the agent used. Practice guidelines recommend pharmacologic intervention in men and women who have had a fragility fracture and whose T scores is −1.5 or lower.. (Rahmani, Morin, 2009)

Selecting the most appropriate agent for an individual patient requires the assessment of the relative value of a particular intervention overall other relevant interventions of choice. With recent additions to the therapeutic armamentarium, physicians now have at their disposal a wide range of osteoporosis treatments. On the other hand, randomized controlled trials are often designed for registration purposes and only include a placebo comparison or one active comparator. Head-to-head comparisons of all available agents are unlikely to become available because of the prohibitive costs and sample size that such a study would require. As a result, information on the efficacy of osteoporotic treatments relative to one another remains limited. (Reginster 2011)

Oral bisphosphonate therapy is considered first-line therapy in the management of osteoporosis. Not all agents are covered by drug benefit formularies, therefore clinicians

should determine which ones are covered in their own setting. Measurement of bone mineral density should be repeated 2 years after initiating treatment to monitor the effectiveness of treatment

Randomized controlled trials provide solid evidence that the bisphosphonates, the SERMs, denosumab, teriparatide and strontium ranelate prevent vertebral fractures compared with placebo. There is also sound evidence for the prevention of hip fracture with alendronate, risedronate, zoledronic acid, and denosumab and strontium ranelate. No single agent is appropriate for all patients and therefore treatment decisions should be made on an individual basis, taking into account all measures of treatment effect and the patient's baseline risk before making informed judgments about the best individual treatment

REFERENCES

Adler Robert A (2009), Osteoporosis: Pathophysiology and clinical management Review from Rizzoli R J Am Diet Assoc (2005); 105:735–741. 102.

Amman P. and Rizzoli R (2003) Bone strength and its determinants;14 (suppl 3):513-518)

Barrett-Connor E, Mosca L, Collins P, et al. (2006), Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women: N Engl J Med. 2006 Jul 13;355(2):125-37

Boonen, Vanderschueren, et al (2006) Osteoporosis management: a perspective based on biosphosponate data methods

Biermasz Nienke R. et al (2004), Long-term skeletal effects of recombinant humar growth hormone (rhGH) alone and rhGH combined with alendronate in GH-deficient adults: a seven-year follow-up study: Clinical Endocrinology Volume 60, Issue 5, pages 568–575, May 2004

Black DM, Delmas PD, Eastell R, et al.(2007), Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis: N Engl J Med. 2007 May 3;356(18):1809-22

Brito CM Moran, 1, Battistella LR 1, 2, 3 2005), Effect of alendronate on bone mineral density in spinal cord injury patients: a pilot study**:** Spinal Cord (2005) 43, 341–348. doi:10.1038/sj.sc.3101725 published online 8 February 2005

Buffum Taylor Rebecca (2011). What Causes Osteoporosis? And Why?. Living with osteoporosis, WebMD:

Burnett Sarah and Pillinger John, GP (2005), Bone densitometry scans (general)

Cadarette Suzanne M. et al (2008), Relative Effectiveness of Osteoporosis Drugs for Preventing Nonvertebral Fracture: Ann Intern Med. 2008; 148:637-646.

Carmona Richard H. 2004), Surgeon General Warns of Bone Break Epidemic: As reported by the Atlantic Journal-Constitution, October 14, 2004

Chan Siew Pheng 1, Scott Boyd B 2, and Sen Shuvayu S 2 (2010), An Asian viewpoint on the use of vitamin D and calcium in osteoporosis treatment: Physician and patient attitudes and beliefs: Chan et al. BMC Musculoskeletal Disorders 2010, 11:248
Available from: http://www.biomedcentral.com/1471-2474/11/248

Chaudhri Tauseef (2006), Identifying nutritional and life style risk factors associated with the development of osteoporosis in women of Asian origin at the Aga khan university, Hospital, Nairobi, Kenya

Cheng J.M.K, MS, Johnson M.A PhD, R. D . Lewis et al 2003), Nutrition Education Issues for Older Adults

Chesnut Charles H. III (2006), The Role of Salmon Calcitonin in the Treatment of Vertebral Fractures: US Musculoskeletal Review, 2006 ;(1):40-45/ 80-82

Chrisopoulos Sadhana Bose Sergio (2010)**,** Benchmarking quality of care for fragility fractures in the South Central SHA area

Collins Karen (2004), how much caffeine is too much

Available from: www.msnbc.msn.com/id/.../ns/.../how-much-**caffeine**-too-much/

.Compston, JE (2001), Bone marrow and bone: a functional unit: (chapter 81):pg 419-447

Cranney, Hanley, et al (2010), Vitamin D in adult health and disease: a review and guideline statement from osteoporosis Canada

Cremers Serge 1,2 and Garnero Patrick 3,4 (2006), Biochemical markers of bone turnover in the clinical development of drugs for osteoporosis and mata-static bone disease: 0 Cummings S. R and Melton L. J (2002), Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002 May 18; 359(9319):1761-7.

Dana Jacobs-Kosmin, MD. (2011), Osteoporosis Treatment & Management
Available from: http://emedicine.medscape.com/article/330598-overview
Dana Jacobs-Kosmin, MD. (2011), Osteoporosis Treatment & Management
Available from: http://emedicine.medscape.com/article/330598-overview
Deplasl, A. Debiais F. Alcalay M. Bontoux D, Thomas P (2004), Bone density, parathyroid hormone, calcium and vitamin D nutritional status of institutionalized elderly subjects: J Nutr Health Aging. 2004; 8(5):400-4.
Deutschmann H. A., Weger M, Weger W, kotanko P. et al (2002), Search for occult secondary osteoporosis: impact of identified possible risk factors on bone mineral density: Journal of Internal Medicine 2002; 252: 389–397

Deane Andrew et al 2007), The impact of vitamin D status on changes in bone mineral density during treatment with bisphosphonates and after discontinuation following long-term use in post-menopausal osteoporosis
Deeks Emma D. and Dhillon Sohita (2011), the effect of PTH (1-84) or strontium ranelate on bone formation markers in postmenopausal women with primary osteoporosis:

Dontas I.A. and Yiannakopoulos C.K. (2007), Risk factors and prevention of osteoporosis-related fractures, Laboratory for Research of the Musculoskeletal System "Th. Garofalides", School of Medicine, University of Athens, Greece: J Musculoskeletal Neuronal Interact 2007; 7(3):268-272

results of a randomized open label clinic trial: Volume: 22, Issue: 9, pages: 2529-2537: Pubmed: 21052638
Elliott Mary (2011), Taking control of osteoporosis to cut down on risk of fracture: Identification of high-risk patients and the provision of interventions are important in the treatment of older people: Nursing Older People, v.23, no.3, 2011 April, p.30(6) (ISSN: 1472-0795)
Available from: http://trove.nla.gov.au/work/151597651
Hayes Helen (2003), Figures available from the National Osteoporosis Foundation at:

www.nof.org/osteoporosis/stats.htm

.Feskanich D, Singh V, Willet WC, et al (2002), Vitamin A intake and hip fractures among postmenopausal women: JAMA. 2002 Jan 2; 287(1):47-54.

Furugren Lena and Laflamme Lucie (2007), Hip fractures among the elderly in a Swedish urban setting: different perspectives on the significance of country of birth

Frampton James E. and Perry Caroline M. (2008), Ibandronate: a review of its use in the management of postmenopausal osteoporosis: Volume: 68, Issue: 18, Pages: 2683-2707

Hottinger Greg MPH, RD, Osteoporosis Prevention: What You Need to Know

Available from: http://www.bestnaturalfoods.com/osteoporosis_prevention.html

Goltzman David, (2008). Largest ever Canadian study on osteoporosis informs health policy: June 18, 2008 - 04:49 in Health & Medicine,

Iwamoto Jun, (2008) Hip fracture protection by alendronate treatment in postmenopausal women with osteoporosis: a review of the literature: Clin Interv Aging. 2008 September; 3(3): 483–489.

Jeffrey Stroup, Michael P. Kane and Asim M. Abu-Baker (2008), Teriparatide in the treatment of osteoporosis: American journal of health system pharmacy AJHP official journal of the American Society of Health System Pharmacists (2008) Volume: 65, Issue: 6, Pages: 532-539. PubMed: 18319498

Kanis J A and Gluer C C, an update on the diagnosis and assessment of osteoporosis with densitometry. Committee of scientific advisors, international osteoporosis foundation: osteop.int 2001; 11: 192-202

Karmen Betty PhD (2011), Osteoporosis drug facts: The untold truth about osteoporosis drugs.

Kiel Douglas P. et al (2007), the effects of Tai Chi on bone mineral density in postmenopausal women: a systematic review. Arch Phys Med Rehabil 2007; 88:673-80.

Lane (2006), Osteoporosis: Is there a rational approach to fracture prevention? Bull NYU Hosp Jt Dis. 2006; 64(1-2):67-71

Latina Health Project (2009-2011):

Available from: http://www.boneporosis.com/ and

http://medicaldictionary.thefreedictionary.com/osteocyte

Lyles KW, Colon-Emeric CS, Magaziner JS, et al. (2007), Zoledronic Acid in Reducing Clinical Fracture and Mortality after Hip Fracture: N Engl J Med. 2007;357:nihpa40967

Mac Laughlin Eric J. and Raehl Cynthia L. (2008), ASHP Therapeutics position statement on the prevention and treatment of osteoporosis in Adults: Am J Health-Syst Pharm. 2008; 65:343-57

Mauck Karen F., MD, MSC, & Clarke Bartl., MD (2006), Diagnosis, Screening, Prevention, and Treatment of Osteoporosis; Mayo Clin Proc. 2006; 81(5):662-672Marshall D, Johnnell O and Wedel H. Brit. Med J. (1996). Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporosis fractures: BMJ. 1996 May 18; 312(7041):1254-9.

Marson Alice E. (2010), Poor health makes osteoporosis common in the U.S

Available from: http://www.naturalnews.com/028826_osteoporosis_health.html

Michael, Abu-Baker, (2008), Teriparatide in the treatment of osteoporosis

Mirzaei Siroos, 1, Zajicek Hubert K, 3 Knoll Peter 1 et al (2003), Effect of Rocaltrol on bone mass in patients with pulmonary disease treated with corticosteroids:
2003, Vol: 40, No 3, pages 251-255

National Osteoporosis Foundation,(2004 & 2005), Clinician's Guide to Prevention and Treatment of Osteoporosis.

Nordin Christopher (2004), From Brittle Bones to Standard Deviations: The Historical Development of Osteoporosis in the Late Twentieth Century

Odawa F., Ojwang S., Muia N, *et al* (2004), The prevalence of postmenopausal osteoporosis in black Kenyan women.]. Obst. Gyn. Eastern and Central Afr. 2004; Review; G. O Oyoo & J. G Kariuki, East A frican Medical Journal Vol.84 November, 2007

Osmanag Mehmet A Aog Lu, Okumus Bakiye, and Osmanag Tayfun Aog Lu et al (2004), The Relationship between Serum Dehydroepiandrosterone Sulfate Concentration and Bone Mineral Density, Lipids, and Hormone Replacement Therapy in Premenopausal and Postmenopausal women: Journal of women's Health. November 2004, 13(9):993-999.DOI:10.1089/JWH.2004.13.993

Osteoclast definition-Medical dictionary definitions of Med terms.MedicineNet.com (2011).
Available from: http://www.medterms.com/script/main/art.asp?articlekey=11794

Ralston S.H (2001), Principles of bone biology.

Rahmani Poupak MD PHD, Morin Suzanne MD MSC (2009), Prevention of osteoporosis- related fractures among postmenopausal women and older men: CMAJ November 24, 2009 vol. 181 no. 11 First published October 19, 2009, doi: 10.1503/cmaj.080709

Recker, et al (2005), Treatment of early postmenopausal women with bisphosphonates: Review Criteria

Reginster, Akesson et al, (2011), Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation working group report

Roche Diagnostics (2009), complete range of automated tests for Osteoporosis: Laboratory product
Availablefrom:http://www.labmate-online.com/news/laboratory-products/3/roche-diagnostics/complete-range-of-automated-tests-for-osteoporosis/6401/

Rosen Hillel N, MD, Rosen Clifford J. MD and Mulder, Jean E MD (2011), Bone physiology and biochemical markers of bone turnover.

Available from http://www.uptodate.com/contents/bone-physiology-and-biochemical-markers-of-bone-turnover

Ruimerman Ronald (2005), Modeling and remodeling in bone tissue. Proefschrift. - ISBN 90-386-2856-0 '

Sharpe Miriam, Noble Stuart et al 2001), Alendronate: An Update of its Use in Osteoporosis: Volume 61 - Issue 7 - pp 999-1039

Spangler Mikayla, Phillips Beth Bryles, Ross Mary B., and Moores Kevin G. (2011), Calcium supplementation in postmenopausal women to reduce the risk of osteoporotic fractures: American Journal of Health-System Pharmacy. 2011; 68(4):309-318. © 2011 American Society of Health-System Pharmacists, Inc

Srivastava, Manish MD, Deal Chad, MD (2002), Osteoporosis in elderly: prevention and treatment: Clin Geriatr Med 18 (2002) 529 – 555

Sutcliffe Anne (2005), an overview of osteoporosis; Nursing Standard. 20, 2, 58-64

Availafrom:http://shsfaculty.swan.ac.uk/GarethNoble/Pharmacology%20Material/Post-Reg%20ACP/Health/Women's%20Health/osteoporosis.pdf

Scottish Intercollegiate Guidelines Network (2005), Preventing osteoporosis

Availablefrom:http://www.consumerreports.org/health/conditions-and-treatments/osteoporosis/what-is-it/preventing-osteoporosis.htm

Toussaint Nigel D., Elder Grahame J., and Kerr Peter G. (2010), A Rational Guide to Reducing Fracture Risk in Dialysis Patients: Article first published online: 22 FEB 2010: DOI: 10.1111/j.1525-139X.2009.00650.x:© 2010 Wiley Periodicals, Inc.

Veasy L George (2001), Is vitamin K deficiency a risk factor for osteoporosis in Crohn's

Available from: www.thelancet.com/journals/lancet/.../PIIS0140-6736(00)X0248-6

Vermaat Hester and Kirtschig Gudula, 2008), Prevention and treatment of glucocorticoid-induced osteoporosis in daily dermatologic practice: International Journal of Dermatology Volume 47, Issue 7, pages 737–742, July 2008

Watts Nelson B., M.D. (2010), Postmenopausal osteoporosis; what's new and what's next?